

1-1-2011

Chemistry of Cyclic Ketene-N,O-Acetals

Yingquan Song

Follow this and additional works at: <https://scholarsjunction.msstate.edu/td>

Recommended Citation

Song, Yingquan, "Chemistry of Cyclic Ketene-N,O-Acetals" (2011). *Theses and Dissertations*. 1054.
<https://scholarsjunction.msstate.edu/td/1054>

This Dissertation - Open Access is brought to you for free and open access by the Theses and Dissertations at Scholars Junction. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of Scholars Junction. For more information, please contact scholcomm@msstate.libanswers.com.

CHEMISTRY OF CYCLIC KETENE-*N,O*-ACETALS

By

Yingquan Song

A Dissertation
Submitted to the Faculty of
Mississippi State University
in Partial Fulfillment of the Requirements
for the Degree of Philosophy
in Chemistry
in the Department of Chemistry

Mississippi State, Mississippi

April 2011

Copyright by
Yingquan Song
2011

CHEMISTRY OF CYCLIC KETENE-*N,O*-ACETALS

By

Yingquan Song

Approved:

Gerald B. Rowland
Assistant Professor of Chemistry
(Major advisor)

Charles U. Pittman, Jr.
Professor of Chemistry
(Dissertation Director)

Keith T. Mead
Professor of Chemistry
(Committee Member)

William P. Henry
Associate Professor of Chemistry
(Committee Member)

Stephen C. Foster
Associate Professor of Chemistry
(Committee Member and Graduate
Coordinator)

Gary L. Myers
Professor of English
Dean of the College of Arts & Sciences

Name: Yingquan Song

Date of Degree: April 30, 2011

Institution: Mississippi State University

Major Field: Chemistry

Major Professor: Gerald B. Rowland

Title of Study: CHEMISTRY OF CYCLIC KETENE-*N,O*-ACETALS

Pages in Study: 144

Candidate for Degree of Doctor of Philosophy

A cyclic ketene acetal is an olefin that is substituted at one end by two electron-donating hetero atoms, like O, N, S, where these heteroatoms are connected together by a chain. Delocalization of the lone pair electrons of the two hetero atoms to the double bond makes the β -carbon (the exocyclic methylene carbon) electron rich and nucleophilic. A major goal of cyclic ketene acetal chemistry is to provide functionalized cyclic ketene acetal monomers as precursors to polymers of desired properties.

The cyclic ketene-*N,O*-acetal 3-methyl-2-methylene-oxazolidine, generated *in situ* from 2-methyl-2-oxazolinium iodide and triethylamine, reacted with aryl isocyanates in refluxing THF to give α,α -bis(*N*-arylamido) lactams via the iodide-catalyzed rearrangement of β,β -bis(*N*-arylamido) cyclic ketene-*N,O*-acetal intermediates. However, similar β,β -bis(*N*-arylamido) cyclic ketene-*N,O*-acetals having two methyl substituents at C-4, did not rearrange due to hindrance of the iodide attack on C-5.

3,4,4-Trimethyl-2-methylene-oxazolidine reacted with aryl chloroformates to form both mono- and di-aryloxycarbonylation adducts. The two methyl groups at C-4

hindered the alternative polymerization route. 3-Methyl-2-methylene-oxazolidine, which does not have two methyl groups at C-4, underwent cationic polymerization under identical conditions.

Benzoylation of 2-methyl-2-oxazoline with benzoyl chloride gave a ring-opened *N,C,O*-trisbenzoylation product via *O*-benzoylation of the *N,C*-bisbenzoylated intermediate, followed by chloride attack on C-5. The *N,C,O*-trisbenzoylated product underwent *N,O*-double debenzoylation by KOH to give the cyclic ketene-*N,O*-acetal, 2-oxazolidin-2-ylidene-1-phenylethanone. This compound (an ambident nucleophile), upon deprotonation, reacted with benzoyl chloride to give the β,β -bisbenzoylated cyclic ketene-*N,O*-acetal, and reacted with phenyl chloroformate to give a novel heterocycle, [1,3]oxazine-2,4-dione. The benzoylation of 2-methyl-2-oxazine gave a similar ring-opened *N,C,O*-trisbenzoylation product.

Reactions of 2-methyl-2-oxazoline, 2,4,4-trimethyl-2-oxazoline and 2-methyl-2-thiazoline with trifluoroacetyl anhydride gave *C*-trifluoroacetylated cyclic ketene-*N,O(S)*-acetals. However, trifluoroacetylation of 2-methyl-2-oxazine gave the β,β -bistrifluoroacetylated cyclic ketene-*N,O*-acetal.

In summary, a novel iodide-catalyzed rearrangement of β,β -bis(*N*-arylamido)-cyclic ketene-*N,O*-acetals was found. The [1,3]oxazine-2,4-dione heterocycle synthesized during this research also demonstrates the synthetic potential of cyclic ketene acetal chemistry in pharmaceutical industry. Functionalization of cyclic ketene acetals based on the chemistry developed in this work will find applications in polymer industry.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Dr. Charles U. Pittman, Jr., my dissertation director, for his guidance, facilities and financial support for the research described in this dissertation. I was impressed by his tireless working style and broad knowledge of science.

I would like to say thanks to Dr. Gerald Rowland, my major advisor, for his help during my dissertation writing and insightful discussions.

Sincere appreciation is extended to my graduate committee members Dr. Keith T. Mead, Dr. William P. Henry and Dr. Stephen C. Foster for their assistance, encouragement and helpful discussions. Dr. William P. Henry is appreciated for helping me with XRD measurement.

Appreciation is also extended to Jinbao He, Aihua Zhou, Chengli Zhu, Guozhong Ye, and all other colleagues and friends for their friendship and valuable help.

Finally, I would like to express my most grateful thanks to my wife Hui Xian and my parents, whose love carried me through my difficult times.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS	ii
LIST OF TABLES	vii
LIST OF FIGURES	viii
LIST OF SCHEMES.....	xi
LIST OF ABBREVIATIONS.....	xiii
CHAPTER	
I. INTRODUCTION	1
II. IODIDE-CATALYZED REARRANGEMENT OF B,B-DI (N-ARYLAMIDO) CYCLIC KETENE-N,O-ACETALS.....	28
Introduction.....	28
Results and discussion	29
Experimental	47
Materials and Instruments.....	47
Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bisphenylamide (195).....	47
Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis- m-tolylamide (196)	48
Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis- [(4-fluorophenyl)-amide (197)].....	49
Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis- [(4-methoxy-phenyl)-amide (198)]	50
Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis- tolylamide (199).....	50
Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis- [(4-cyanophenyl) amide (200) and <i>N,N'</i> -bis-(4-cyanophenyl)-2- (3-methyloxazolidin-2-ylidene)-malonamide (192)]	51

Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis- [(4-trifluoromethylphenyl)-amide (201) and 2-(3- methyloxazolidin-2-ylidene)- <i>N,N'</i> -bis-(4- trifluoromethylphenyl)-malonamide (193)	52
Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis- [(4-trifluoromethylphenyl)-amide (201) and 2-(3- methyloxazolidin-2-ylidene)- <i>N,N'</i> -bis-(4- trifluoromethylphenyl)-malonamide (193) by refluxing in THF	53
Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis- [(2-bromophenyl)-amide] (202) and <i>N,N'</i> -bis-(2-bromophenyl)- 2-(3-methyloxazolidin-2-ylidene)-malonamide (194)	53
Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis- [(2-bromophenyl)-amide] (202) using 1,4-dioxane as solvent	54
Preparation of 2-(3-methyloxazolidin-2-ylidene)- <i>N,N'</i> -diphenyl- malonamide (191)	55
Preparation of <i>N,N'</i> -diphenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)- malonamide (74)	55
Preparation of <i>N,N'</i> -di- <i>m</i> -tolyl-2-(3,4,4-trimethyloxazolidin-2- ylidene)-malonamide (183)	56
Preparation of <i>N,N'</i> -bis-(4-fluorophenyl)-2-(3,4,4-trimethyloxazolidin- 2-ylidene)-malonamide (184)	57
Preparation of <i>N,N'</i> -bis-(4-methoxyphenyl)-2-(3,4,4- trimethyloxazolidin-2-ylidene)-malonamide (185)	57
Preparation of <i>N,N'</i> -Di- <i>p</i> -tolyl-2-(3,4,4-trimethyloxazolidin-2- ylidene)-malonamide (186)	58
Preparation of <i>N,N'</i> -bis-(4-cyanophenyl)-2-(3,4,4-trimethyloxazolidin- 2-ylidene)-malonamide (187)	58
Preparation of <i>N,N'</i> -bis-(4-trifluoromethylphenyl)-2-(3,4,4- trimethyloxazolidin-2-ylidene)-malonamide (188)	59
Preparation of <i>N,N'</i> -bis-(2-bromophenyl)-2-(3,4,4-trimethyloxazolidin- 2-ylidene)-malonamide (189)	60
Bu ₄ NI catalyzed rearrangement of 2-(3-methyloxazolidin-2-ylidene)- <i>N,N'</i> -diphenyl-malonamide (191)	60
Preparation of <i>N</i> -(2-bromophenyl)-2-(3,4,4-trimethyloxazolidin-2- ylidene)-acetamide (210)	61
Attempted intramolecular Heck reaction of <i>N</i> -(2-bromophenyl)-2- (3,4,4-trimethyloxazolidin-2-ylidene)-acetamide (210)	62
Preparation of 1-phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)- ethanone (90) from <i>in situ</i> generated 3,4,4-trimethyl-2- methylene-oxazolidine (27)	63

III. REACTIONS OF CYCLIC KETENE-*N,O*-ACETALS WITH CHLOROFORMATES.....63

Introduction.....	63
Results and discussion	65

Experimental	72
Preparation of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid ethyl ester (219)	72
Preparation of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid phenyl ester (220) and 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid diphenyl ester (221)	73
Preparation of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid 4-methoxyphenyl ester (222) and 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid bis-(4-methoxyphenyl) ester (223)	76
Preparation of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid 4-nitrophenyl ester (225) and 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid bis-(4-nitrophenyl) ester (226)	79
Reaction of cyclic ketene- <i>N,O</i> -acetal 56 with phenyl chloroformate	80
Reaction of cyclic ketene- <i>N,O</i> -acetal 56 with <i>p</i> -methoxyphenyl chloroformate	81
Reaction of ethyl chloroformate with <i>in situ</i> generated cyclic ketene- <i>N,O</i> -acetal 27	81
Reaction of <i>p</i> -nitrophenyl chloroformate with <i>in situ</i> generated cyclic ketene- <i>N,O</i> -acetal 27	81
 IV. BENZOYLATION OF 2-METHYL-2-OXAZINE AND 2-METHYL-2-OXAZOLINE	83
Introduction	83
Results and discussion	84
Experimental	92
Preparation of 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(<i>Z</i>)-propenyl benzoate (238) by benzylation of 2-methyl-2-oxazine (237) in refluxing THF	92
Preparation of <i>N</i> -acetyl- <i>N</i> -(3-hydroxypropyl)-benzamide (242) by benzylation of 2-methyl-2-oxazine (237) with benzoic anhydride	94
Attempted preparation of 2-(3-benzoyl-[1,3]oxazinan-2-ylidene)-1-phenylethanone (239) by benzylation of 2-methyl-2-oxazine (237) at room temperature	96
Preparation of 3-[benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (244) by benzylation of 2-methyl-2-oxazoline (84) in THF	97
Preparation of 3-[benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (244) by benzylation of 2-methyl-2-oxazoline (84) with 3.3 equivalents of benzoyl chloride in THF	99
Preparation of 3-(4-chlorophenyl)-3-oxopropionic acid 2-(4-chlorobenzoylamino)-2-methyl-propyl ester (246)	100
 V. TRIFLUOROACETYLATION OF 2-METHYL-2-OXAZOLINES, 2-METHYL-2-THIAZOLINE AND 2-METHYL-2-OXAZINE	102

Introduction.....	102
Results and discussion	103
Experimental	116
Preparation of (<i>E</i>)-1,1,1-trifluoro-3-oxazolidin-2-ylidene-propan-2-one (254).....	116
Preparation of (<i>E</i>)-3-(4,4-dimethyloxazolidin-2-ylidene)-1,1,1- trifluoropropan-2-one (255).....	117
Preparation of (<i>E</i>)-1,1,1-trifluoro-3-thiazolidin-2-ylidene-propan-2-one (256).....	118
Preparation of 1,1,1,5,5,5-hexafluoro-3-[1,3]oxazinan-2-ylidene- pentane-2,4-dione (265).....	119
Preparation of 1,1,1,5,5,5-hexafluoro-3-[1,3]oxazinan-2-ylidene- pentane-2,4-dione (265), using DIPEA as the base	120
Preparation of 4,4,4-trifluoro-1-phenyl-2-(3,4,4-trimethyloxazolidin-2- ylidene)-butane-1,3-dione (286)	121
 VI. REACTIONS OF 2-OXAZOLIDIN-2-YLIDENE-1- PHENYLETHANONE AND ITS ANION WITH ELECTROPHILES	123
Introduction.....	123
Results and discussion.....	125
Experimental	135
Preparation of 2-oxazolidin-2-ylidene-1-phenylethanone (291) from debenzoylation of 3-[benzoyl-(2-chloroethyl)-amino]-3-oxo-1- phenylpropenyl benzoate (244).....	135
Benzoylation of 2-oxazolidin-2-ylidene-1-phenylethanone (291) with benzoyl chloride.....	136
Benzoylation of cyclic ketene- <i>N,O</i> -acetal 291 with benzoic anhydride.....	136
DMAP-catalyzed benzoylation of cyclic ketene- <i>N,O</i> -acetal 291 with benzoic anhydride	137
Preparation of 2-oxazolidin-2-ylidene-1,3-diphenylpropane-1,3-dione (295) from benzoylation of ambident anion 293	137
Preparation of carbonic acid 3-[(2-chloroethyl)-phenoxy-carbonyl- amino]-3-oxo-1- phenylpropenyl ester phenyl ester (298) by benzoylation of 2-oxazolidin-2-ylidene-1-phenylethanone (291) in CH ₃ CN	138
Preparation of 3-(2-hydroxyethyl)-6-phenyl-[1,3]oxazine-2,4-dione (302) from the reaction of ambident anion (293) with phenyl chloroformate.....	139
 REFERENCES	141

LIST OF TABLES

2.1	Reactions of <i>in situ</i> generated cyclic ketene- <i>N,O</i> -acetal 27 with isocyanates ^a	30
2.2	Reactions of <i>in situ</i> generated cyclic ketene- <i>N,O</i> -acetal 56 with isocyanates ^a	32
2.3	Comparison of carbon-carbon double bond lengths and twist angles ^a for 191 and 207	42
3.1	Comparison of carbon-carbon double bond lengths and twist angles ^a for 222 and 223	69

LIST OF FIGURES

1.1	Cyclic ketene- <i>O,O</i> -, - <i>N,O</i> -, - <i>N,S</i> - and - <i>N,N</i> -acetals	1
2.1	Crystal structure of α,α -bis(<i>N</i> -phenylamido)- γ -lactam 195 , CCDC: 794113.....	34
2.2	Crystal structure of 2-(3-methyloxazolidin-2-ylidene)- <i>N,N'</i> -diphenyl-malonamide 191 . CCDC: 794114.....	35
2.3	Electron withdrawing cyano groups reduce the electron density at the β -carbon	38
2.4	The 4,4-dimethyl groups prevent the iodide attack on C-5 of 74	39
2.5	The crystal structure of 2-oxazolidin-2-ylidene- <i>N,N'</i> -diphenyl-malonamide (207). CCDC: 796900	42
2.6	The crystal structure of 1,3-bis-(2-bromophenyl)-1-[2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetyl]-urea (212)	62
3.1	¹ H NMR of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid phenyl ester (220)	74
3.2	¹³ C NMR of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid phenyl ester (220)	75
3.3	¹ H NMR of 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid diphenyl ester (221)	75
3.4	¹³ C NMR of 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid diphenyl ester (221)	76
3.5.	Crystal structure of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid 4-methoxyphenyl ester (222). CCDC: 796898	77
3.6.	Crystal structure of 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid bis-(4-methoxyphenyl) ester (223). CCDC: 796895.....	78
3.7	Crystal structure of di-(4-methoxyphenyl) carbonate 224	79

4.1	¹ H NMR of 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(Z)-propenyl benzoate (238)	93
4.2	¹³ C NMR of 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(Z)-propenyl benzoate (238)	93
4.3	Crystal structure of 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(Z)-propenyl benzoate (238). CCDC 796896	94
4.4	¹ H NMR of <i>N</i> -acetyl- <i>N</i> -(3-hydroxypropyl)-benzamide (242).....	95
4.5	¹³ C NMR of <i>N</i> -acetyl- <i>N</i> -(3-hydroxypropyl)-benzamide (242).....	96
4.6	¹ H NMR of 3-[benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (244).....	98
4.7.	¹³ C NMR of 3-[benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (244).....	99
4.8.	The crystal structure of 3-(4-chlorophenyl)-3-oxopropionic acid 2-(4-chlorobenzoylamino)-2-methyl-propyl ester (246).....	101
5.1	Cyclic ketene- <i>N,O</i> -acetals 254-256 and their corresponding anions 257-259 are ambident nucleophiles	111
5.2.	The crystal structure of 3-(4,4-dimethyloxazolidin-2-ylidene)-1,1,1-trifluoropropan-2-one (255). CCDC: 796901	112
5.3	The crystal structure of 1,1,1,5,5,5-hexafluoro-3-[1,3]oxazinan-2-ylidene-pentane-2,4-dione (265). CCDC: 796902.....	112
5.4	β-Keto cyclic ketene- <i>N,O</i> -acetal 90 is less nucleophilic at its β-carbon than its precursor 27	113
5.5	¹ H NMR of 3-(4,4-dimethyloxazolidin-2-ylidene)-1,1,1-trifluoropropan-2-one (255)	117
5.6	¹³ C NMR of 3-(4,4-dimethyloxazolidin-2-ylidene)-1,1,1-trifluoropropan-2-one (255)	118
5.7	¹ H NMR of 1,1,1,5,5,5-hexafluoro-3-[1,3]oxazinan-2-ylidene-pentane-2,4-dione (265).....	119
5.8	¹ H NMR of 1,1,1,5,5,5-hexafluoro-3-[1,3]oxazinan-2-ylidene-pentane-2,4-dione (265).....	120

5.9	The crystal structure of [1,1-dimethyl-2-(3-oxo-3-phenylpropionyloxy)-ethyl]-methyl-ammonium trifluoroacetate (287).....	122
6.1	291 and its deprotonated form 293 are ambident nucleophiles	127
6.2	The crystal structure of 2-oxazolidin-2-ylidene-1-phenylethanone (291). CCDC: 796899	135
6.3	The crystal structure of 3-(2-hydroxyethyl)-6-phenyl-[1,3]oxazine-2,4-dione (302). CCDC: 796903	140

LIST OF SCHEMES

1.1	Multiple reaction pathways of acid-initiated cyclic ketene-O,O-acetal polymerization	6
1.2	Possible arylation of 1,2-dimethyl-2-imidazole.....	19
2.1	Reaction of cyclic ketene- <i>N,O</i> -acetal 27 , generated <i>in situ</i> from 2,3,4,4-tetramethyl-2-oxazolinium iodide (182) and triethylamine, and phenyl isocyanate.....	29
2.2	Proposed mechanism for iodide-catalyzed rearrangement of 2-(3-methyloxazolidin-2-ylidene)- <i>N,N'</i> -diphenyl-malonamide (191)	37
2.3	Proposed mechanism for iodide-catalyzed rearrangement of [(<i>N</i> -aziridinomethylthio) methylene]-2-oxindoles (204).....	40
2.4	A suggested mechanism for formation of <i>N</i> -(2-bromophenyl)-acetamide (213).....	45
3.1	A suggested mechanism for polymerization of cyclic ketene- <i>N,O</i> -acetal 56	70
3.2	Proposed mechanism for reaction of cyclic ketene- <i>N,O</i> -acetal 27 with phenyl chloroformate	71
4.1	Suggested route to <i>N,C,O</i> -tribenzoylated, ring-opened product 238 from <i>N,C</i> -dibenzoylated cyclic ketene- <i>N,O</i> -acetal 239	85
4.2	Benzoylation of 2-methyl-2-oxazine (237) using benzoic anhydride may stop at the <i>N,C</i> -dibenzoylation stage.....	86
4.3	Hydrolysis of 2-[3-(4-chlorobenzoyl)-4,4-dimethyloxazolidin-2-ylidene]-1-(4-chlorophenyl)-ethanone (245)	91
5.1	A possible mechanism for <i>N</i> -deacylation of 251-253 by water.....	105
5.2	Six and seven-membered enaminoesters undergo <i>N</i> -acylation, β -acylation and <i>N</i> -deacylation by chloride anion to give β,β -disubstituted adducts 270 and 272	108

5.3	<i>C</i> -alkylation of the pyrrolidine enamine 277 involves formation of a trigonal nitrogen on a five-membered ring, which is easier than its six-membered analog	109
5.4	Six-membered <i>N,C</i> -bistrifluoroacetylated cyclic ketene- <i>N,O</i> -acetal 281 undergoes a third acylation at its β -carbon	110
5.5	Five-membered <i>N,C</i> -bistrifluoroacetylated cyclic ketene- <i>N,O</i> -acetal 251 resists a third acylation at its β -carbon.....	110
5.6	Hydration of β,β -disubstituted push-pull cyclic ketene- <i>N,O</i> -acetal 286	115
6.1	A possible route to 291 from <i>N</i> -debenzoylation of 234	124
6.2	A possible route to cyclic ketene- <i>N,O</i> -acetal 291 from 244	126
6.3	A suggested route to cyclic ketene- <i>N,O</i> -acetal tautomer 295 from 291	130
6.4	Reason why <i>N,C</i> -dibenzoylation product 234 is not observed	131
6.5	A suggested route to carbonic acid 3-[(2-chloroethyl)-phenoxy-carbonyl-amino]-3-oxo-1-phenylpropenyl ester phenyl ester (298)	132
6.6	A suggested route to 302	134

LIST OF ABBREVIATIONS

DCM: dichloromethane

DIPEA: *N,N*-diisopropylethylamine

DMAP: 4-dimethylaminopyridine

THF: tetrahydrofuran

TLC: thin layer chromatography

XRD: X-ray diffraction

CHAPTER I

INTRODUCTION

A cyclic ketene acetal is an olefin that is substituted at one end by two electron-donating hetero atoms, like O, N, S, where these heteroatoms are connected together by a chain.¹ Delocalization of the lone pair electrons of the two hetero atoms to the carbon-carbon double bond makes the β -carbon (defined herein as the exocyclic methylene carbon) electron rich and nucleophilic. This is illustrated by **1-4** in Figure 1.1.

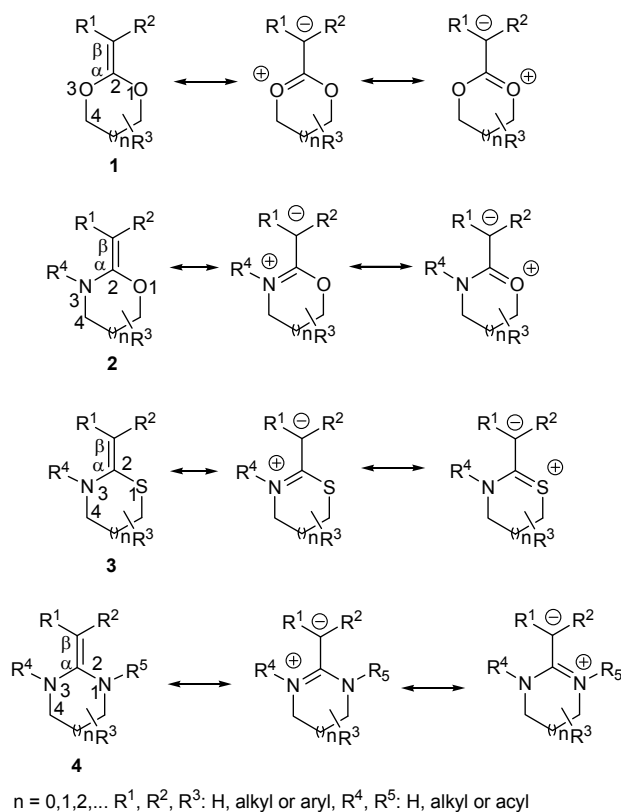
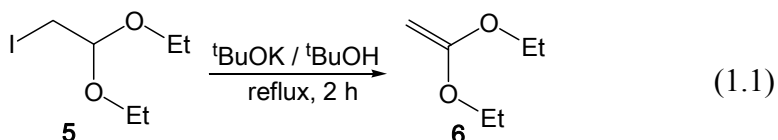


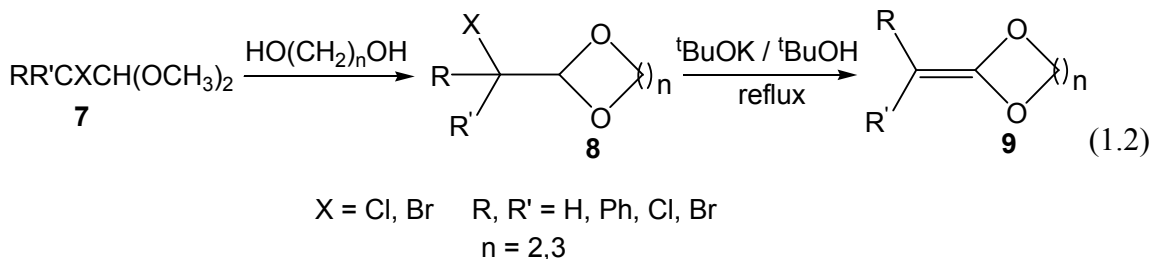
Figure 1.1 Cyclic ketene-*O,O*-, -*N,O*-, -*N,S*- and -*N,N*-acetals

A review of cyclic ketene acetal chemistry is provided to give a background on what is now known about these interesting reactive systems. A large part of this background shows chemistry developed in Pittman's group. This sets the stage for the new work reported in this dissertation.

McElvain was the pioneer of ketene acetal research.² 1,1-Diethoxy-2-iodo-ethane (**5**) was subjected to a strong base to induce elimination of HI to form a ketene acetal, 1,1-diethoxy-ethene (**6**) (Equation 1.1).³



A short time thereafter, McElvain made the first example of cyclic ketene acetal **9**.¹ 1,1-Dimethoxy-2-halo-ethane (**7**) and its 2-substituted derivatives reacted with 1, ω -diols via acetal exchange reactions to form cyclic acetals **8**, which underwent elimination of HX to form **9** (Equation 1.2).

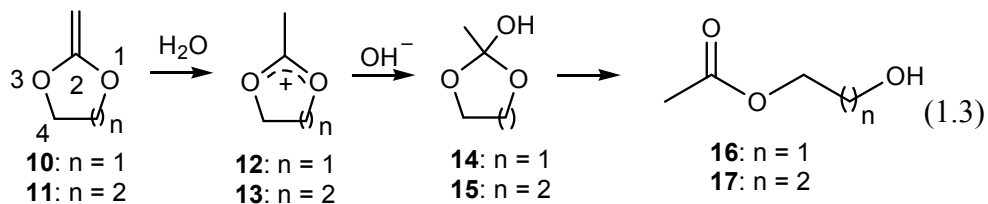


As mentioned above, in addition to oxygen, the electron donating hetero atoms of a cyclic ketene acetal can be nitrogen or sulfur. The third group bound to the nitrogen is usually an alkyl, aryl, acyl group or a hydrogen atom. The β -carbon and the ring can carry substituents. If the β -carbon is substituted by electron withdrawing groups, a “push-pull” structure is formed due to the coupling between electron donation (from O, N, or S) on one end of the carbon-carbon double bond and electron withdrawal on the other end.

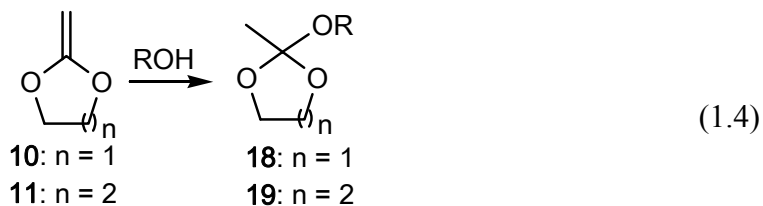
“Push-pull” compounds have an elongated, polarized exocyclic carbon-carbon double bond and find applications in organic nonlinear optical materials.⁴

The chemistry of a cyclic ketene acetal results from its highly polarized carbon-carbon double bond and the nucleophilic terminal carbon's reactivity towards a variety of electrophiles. A proton is the simplest electrophile that reacts with cyclic ketene acetals. Protonation of cyclic ketene-*O,O*-acetals **10** and **11** by Brønsted acids HY (HY = carboxylic acids, alcohols, water, etc.) at the β-carbon leads to stable 1,3-dioxonium intermediates **12** and **13**, respectively, which are susceptible to nucleophilic attack via multiple paths.

Cyclic ketene-*O,O*-acetals **10** and **11** reacted with water to give hydroxy alkyl esters **16** and **17**, respectively (Equation 1.3),¹ probably via intermediates **14** and **15**, respectively.



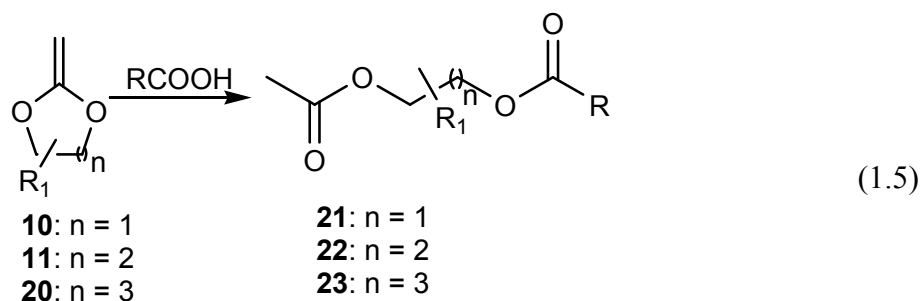
Cyclic ketene-*O,O*-acetals **10** and **11** react with alcohols to produce stable mixed orthoesters **18** and **19**, respectively (Equation 1.4).¹



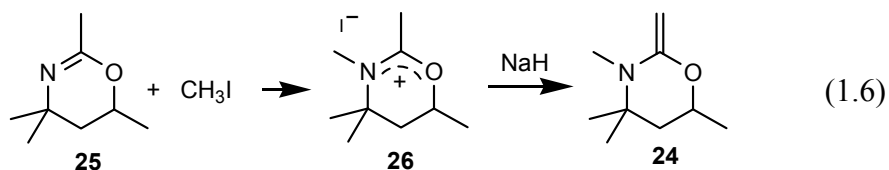
Five, six and seven-membered cyclic ketene-*O,O*-acetals **10**, **11** and **20** reacted with carboxylic acids to give mixed diesters **21-23** (Equation 1.5).⁵ **10**, **11** and **20** must be

added into carboxylic acids (neat or THF solution) to ensure that **21-23** be formed.

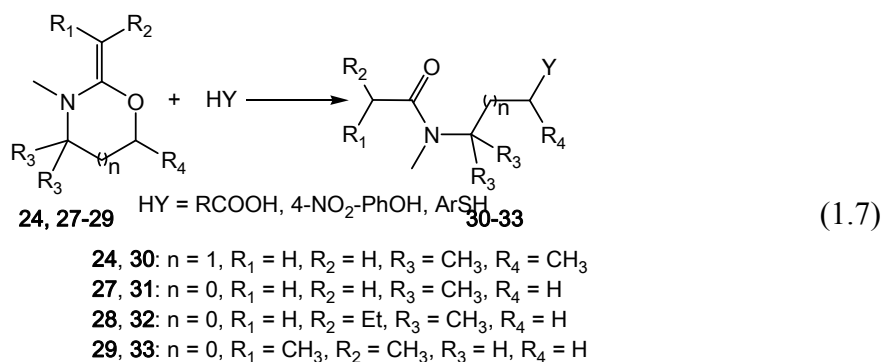
Otherwise, acid-initiated ring-opening polymerizations dominate.⁵



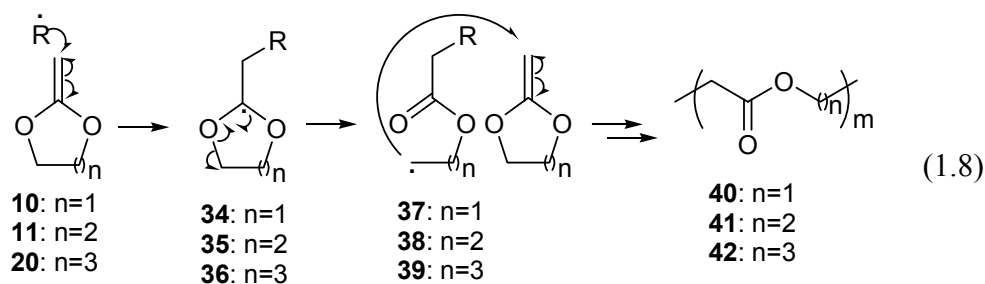
Meyers pioneered the synthesis of cyclic ketene-*N,O*-acetals from 2-oxazolines or 2-oxazines via *N*-methylation and deprotonation with NaH. For example, cyclic ketene-*N,O*-acetal **24** was made from 2,4,4,6-tetramethyl-2-oxazine (**25**) (Equation 1.6).⁶



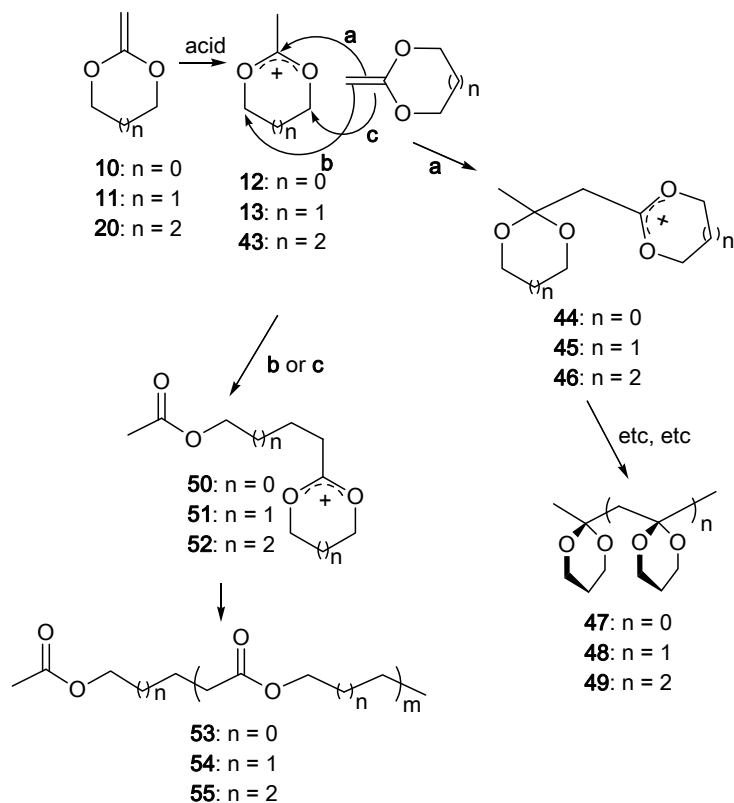
Cyclic ketene-*N,O*-acetals **24**, **27**, **28** and **29** reacted with carboxylic acids, 4-nitrophenol and arylthiols to form ring-opened amidoesters, amidoaryl ether and amidothioethers **30-33**, respectively (Equation 1.7).⁷ These reactions involved proton transfer from HY (HY = RCOOH, 4-NO₂-PhOH, ArSH) to the β-carbon followed by Y⁻ nucleophilic attack at the ring carbon adjacent to the ring oxygen and ring-opening.



Cyclic ketene acetals **10**, **11** and **20** undergo radical ring-opening polymerization upon initiation by AIBN.⁸ Tertiary carbon radicals **34-36**, flanked by two heteroatoms (Equation 1.8), are formed as the intermediate. Radical propagation through opening of the ring oxygen - carbon bond led to polyesters **40-42**. Seven-membered cyclic ketene acetals undergo complete ring-opening. Five- and six-membered cyclic ketene acetals, however, undergo both radical ring-opening and classic 1,2-vinyl polymerization. If a phenyl group is present on the 4-position (radical center) of **37**, the degree of ring-opening is enhanced.

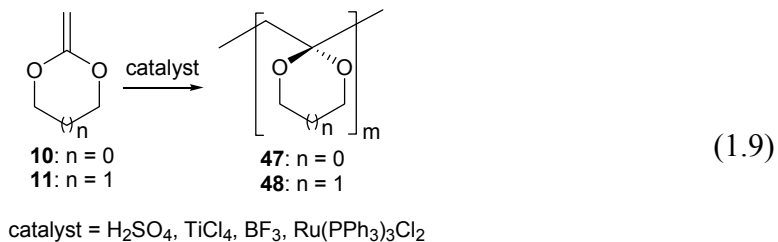


Pittman's group explored extensively Brønsted acid and Lewis acid initiated cationic polymerization of cyclic ketene-*O,O*-acetals.^{9a-k} Cationic polymerization is shown in Scheme 1.1 by the conversion of **10**, **11** and **20** to **47-49** or **53-55**. Upon formation of 1,3-dioxonium intermediates **12**, **13** and **43**, the second cyclic ketene-*O,O*-acetal monomer can attack by three possible pathways. Path **a** gives ring-retained 1,2-vinyl polymers **47-49**,^{9k} whereas paths **b** and **c** give ring-opened polyesters **53-55**.⁹ⁱ



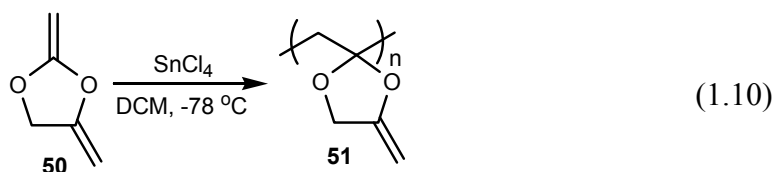
Scheme 1.1 Multiple reaction pathways of acid-initiated cyclic ketene-*O,O*-acetal polymerization

Cyclic ketene-*O,O*-acetal **10** and **11** underwent 1,2-vinyl addition polymerization upon initiation by either Brønsted or Lewis acids to give ring-retained polymer **47** and **48** (Equation 1.9).^{9k}

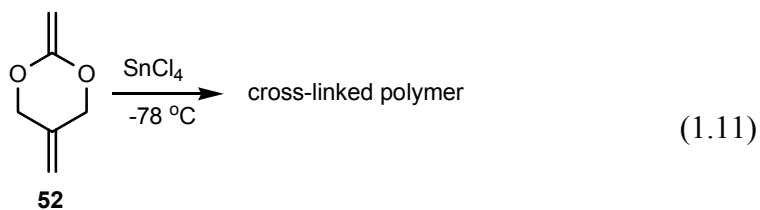


2,4-Dimethylene-1,3-dioxolane (**50**), at low concentrations in DCM, was selectively polymerized at $-78\text{ }^\circ\text{C}$ through the 2-methylene group to afford vinyl ether-pendent polymers **51**. This reaction was catalyzed by the Lewis acid SnCl_4 (Equation

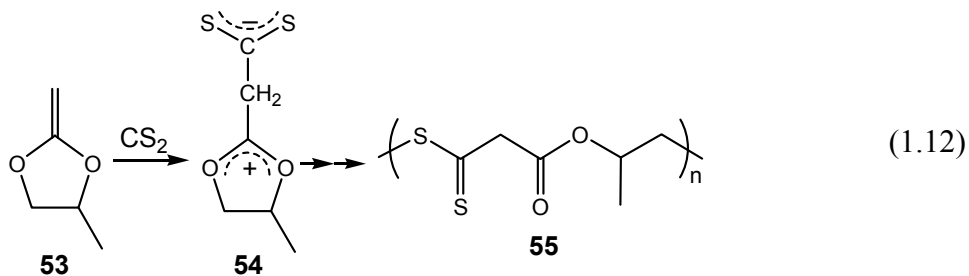
1.10).¹⁰ Higher monomer concentrations, higher temperatures and longer reaction times gave rise to cross-linked polymers.



Under the same conditions (-78 °C), the polymerization of 2,5-dimethylene-1,3-dioxane (**52**) (Equation 1.11) gave only cross-linked polymer. It was presumed that one of the two double bonds of **50**, conjugated through the oxygen atom, acts as an electron-donating group to decrease polymerizability of the 4-methylene function to produce soluble polymer,¹⁰ The two double bonds of **52**, not conjugated one another, however, polymerize simultaneously to afford cross-linked polymer.

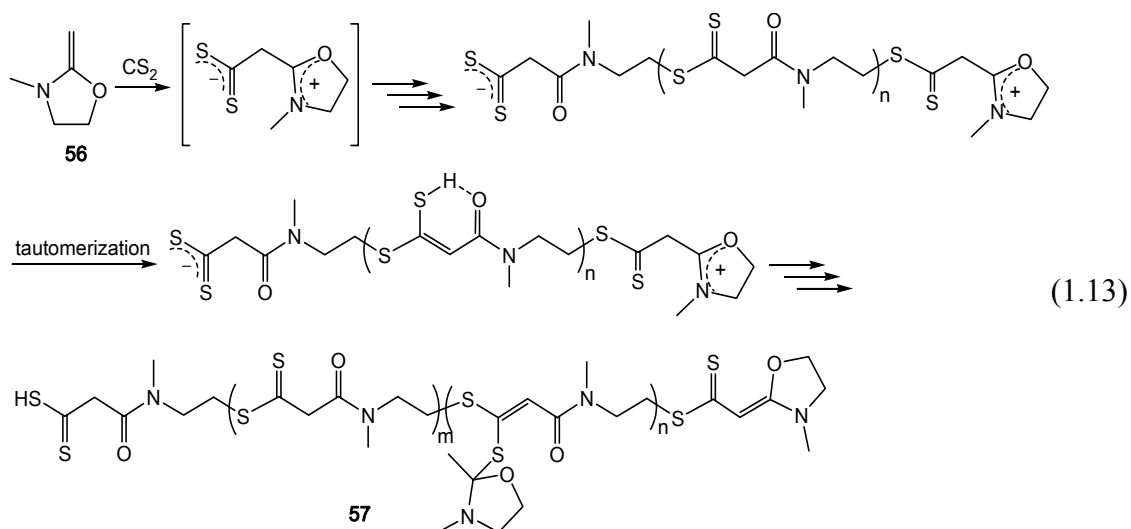


Cyclic ketene-*O,O*-acetal **53** underwent copolymerization with CS₂ to give **55** through a zwitterionic intermediate **54** (Equation 1.12).¹¹

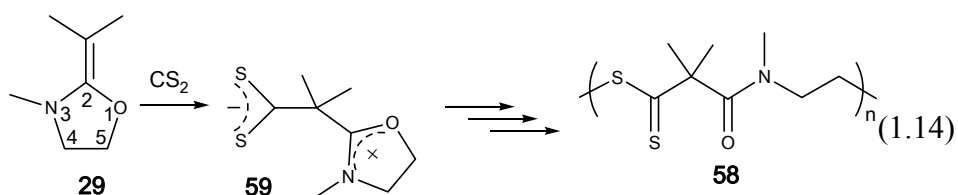


Five-membered cyclic ketene-*N,O*-acetal, 3-methyl-2-methylene-1,3-oxazolidine (**56**), in analogy to the reaction of **53** with CS₂, underwent copolymerization with CS₂ to give copolymer **57**.¹² The tautomerization to the enethiol structure followed by 1,2-vinyl

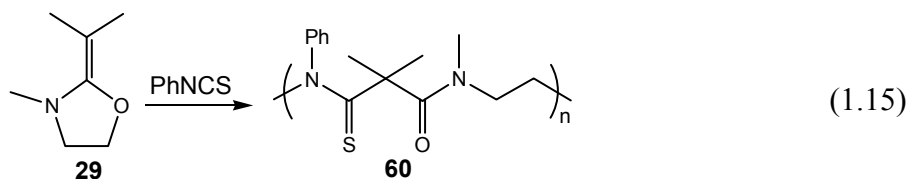
addition of thiol moiety to cyclic ketene-*N,O*-acetal monomer gave rise to polymers with a cyclic ketene-*N,O*-acetal to CS₂ ratio of 65/35 (Equation 1.13).



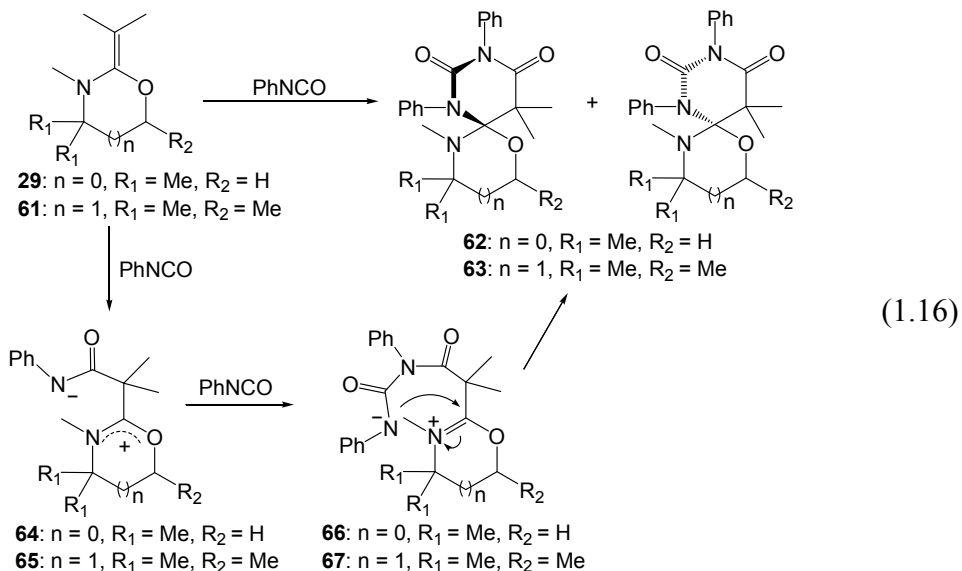
However, copolymerization of 2-isopropylidene-3-methyl-1,3-oxazolidine (**29**) and CS₂ gave the 1:1 alternating copolymer **58** (Equation 1.14).¹² The zwitterionic intermediate **59**, formed by the reaction of **29** and carbon disulfide, continuously self-reacts by the attack of the dithiocarboxylate anion of one zwitterionic intermediate on the C-5 of another zwitterionic intermediate. The lack of β-protons precluded both the tautomerization to the enethiol structure (and the subsequent 1,2-vinyl addition to cyclic ketene-*N,O*-acetal monomers) and zwitterion termination through intermolecular proton transfer from the β-carbon of one zwitterion to the dithiocarboxylate anion of another zwitterion. This led to a higher molecular weight polymer.



Similarly, copolymerization of **29** and phenyl isothiocyanate gave 1:1 alternating copolymer **60** (Equation 1.15).¹³

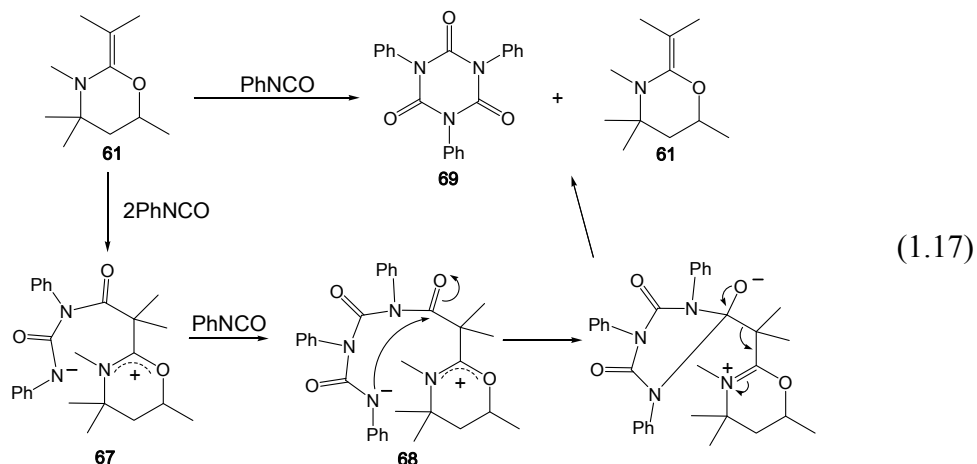


Reactions between β,β -disubstituted cyclic ketene-*N,O*-acetals **29** or **61** with isocyanates displayed multiple paths depending on temperature. At room temperature, these reactions gave spirobicyclic compounds **62-63** (Equation 1.16).¹⁴ The lack of hydrogens on the β -carbons of the zwitterions **64-65** precluded the intermolecular proton transfer leading to zwitterion termination. Thus, the negatively charged nitrogens of **64-65** attacked a second isocyanate. This formed new zwitterions **66-67**, which ring-closed to **62-63**, respectively.

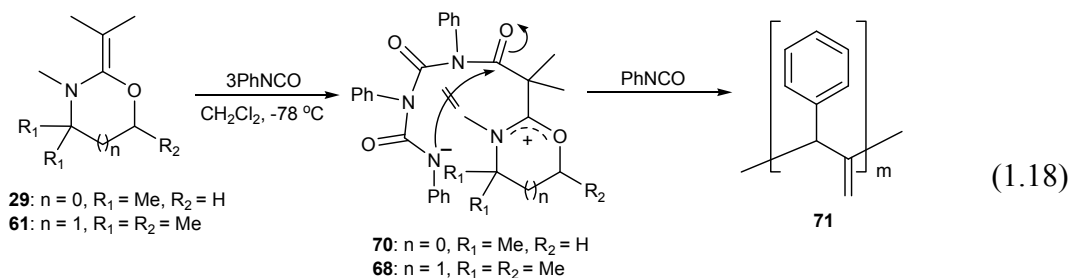


In contrast to its behavior at ambient temperature, six-membered cyclic ketene-*N,O*-acetal **61** catalyzed cyclotrimerization of aryl isocyanates at -25 °C (Equation 1.17).¹⁴ The zwitterion intermediate **67** reacted with a third phenyl isocyanate to form

new zwitterion **68** instead of undergoing ring closure to form **63**. **68** underwent an intramolecular nucleophilic attack, via its negatively charged nitrogen, on the keto function adjacent to the β -carbon, followed by elimination of cyclic ketene-*N,O*-acetal **61**, to give 1,3,5-triphenyl-[1,3,5]triazinane-2,4,6-trione **69**.

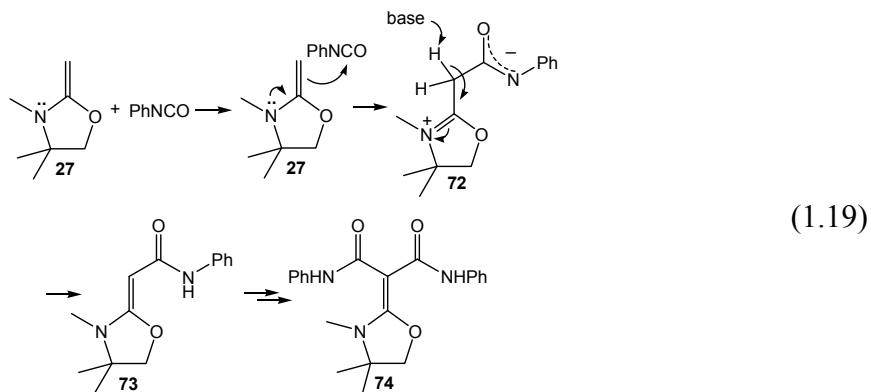


A third pathway was found if the temp was lowered to $-78\text{ }^{\circ}\text{C}$.¹⁴ Cyclic ketene-*N,O*-acetal **29** and **61** initiated aryl isocyanate polymerization. The zwitterion intermediate **70**, **68** reacted faster with more phenyl isocyanate than the rate of internal nucleophilic attack leading to **69**. Successive additions of phenyl isocyanate led to polymer **71** (Equation 1.18).

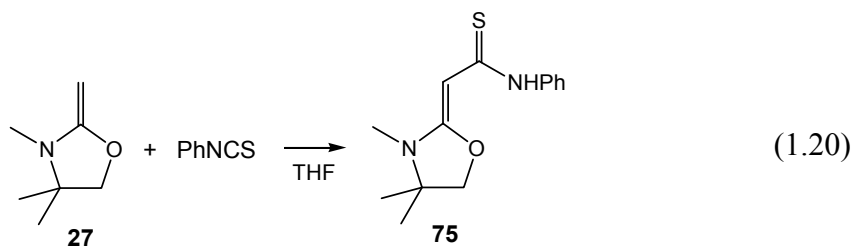


Five-membered cyclic ketene-*N,O*-acetal **27** with no substituents on the β -carbon reacted with phenyl isocyanate to give zwitterion intermediate **72**. Intermolecular proton transfer (between **27** and zwitterion intermediate **72**, for example) leads to 'push-pull'

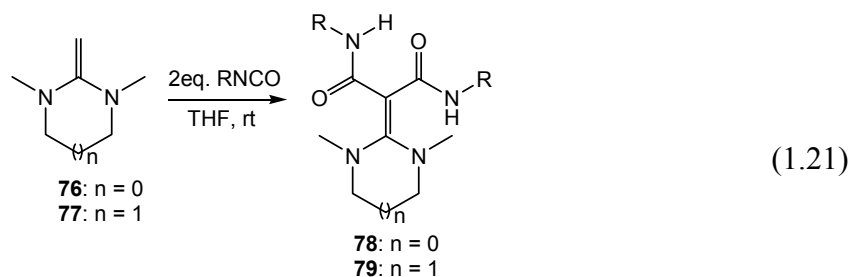
mono-adducts **73**. If more than the stoichiometric amount of phenyl isocyanate was used, **73** reacted further to give bis-adduct **74** (Equation 1.19).¹⁴ Six-membered cyclic ketene-*N,O*-acetals unsubstituted at the β -carbon reacted with phenyl isocyanate in a similar manner.¹⁴



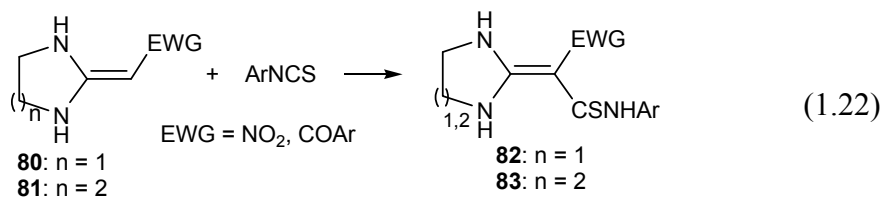
Cyclic ketene-*N,O*-acetal **27** reacted with phenyl isothiocyanate, a weaker electrophile than phenyl isocyanate, giving rise to β -monosubstituted product **75** (Equation 1.20).¹⁴ Cyclic ketene-*N,S*-acetals reacted with phenyl isothiocyanate in a similar manner to give the corresponding mono adducts.¹⁴



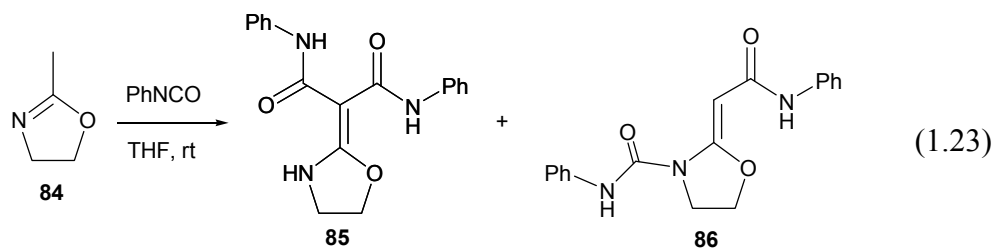
The more nucleophilic cyclic ketene-*N,N*-acetals **76-77** reacted with two equivalents of isocyanates to give β,β -disubstituted product **78-79** (Equation 1.21).¹⁵



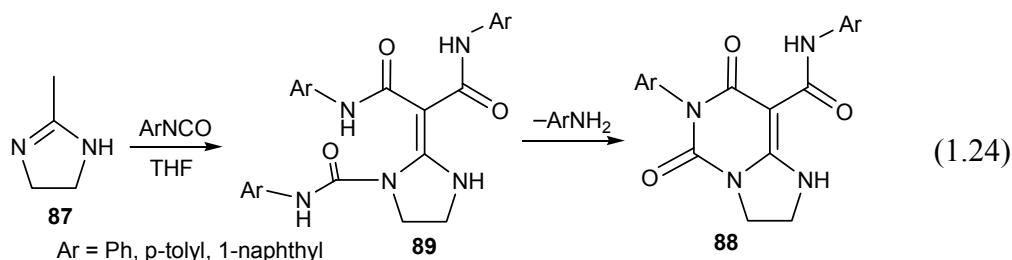
Cyclic ketene-*N,N*-acetals **80-81**, which carry an electron withdrawing group at the β -carbon, reacted with phenyl isothiocyanate to form **82** and **83**, respectively (Equation 1.22),¹⁶ despite the diminished nucleophilicity at the β -carbons of **80** and **81**.



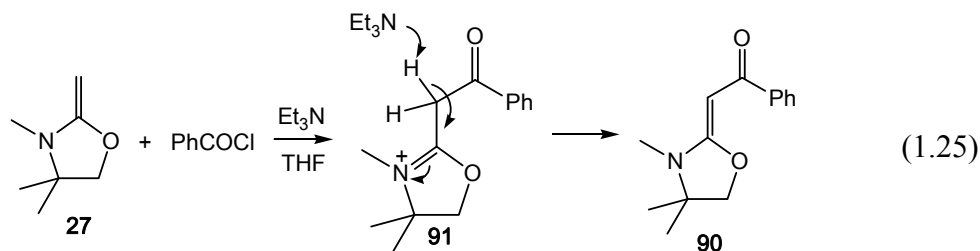
2-Methyl-2-oxazoline (**84**) reacted with phenyl isocyanate at ambient temperature to form β,β -bis(*N*-phenylamido) cyclic ketene-*N,O*-acetal **85** (Equation 1.23) as the major product and *N,C*-bis(*N*-phenylamido) cyclic ketene-*N,O*-acetal **86** as the minor product.¹⁷ **84** reacted with PhNCO at 0 °C preferentially to produce **86**. It was speculated that **86** undergoes a thermal rearrangement to give rise to **85**.



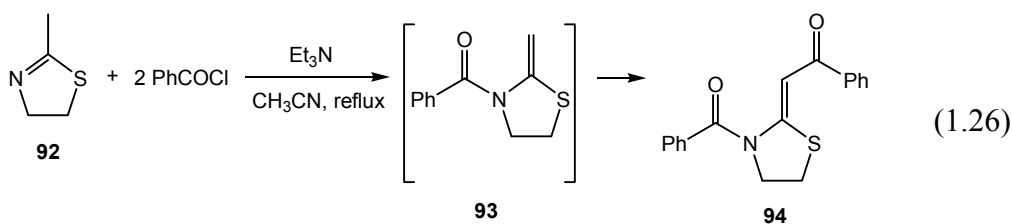
In contrast to **84**, imidazoline **87** reacted with aryl isocyanates to form fused heterocycles **88** through an *N,C,C*-(*N*-phenylamido) intermediate **89** (Equation 1.24).¹⁸



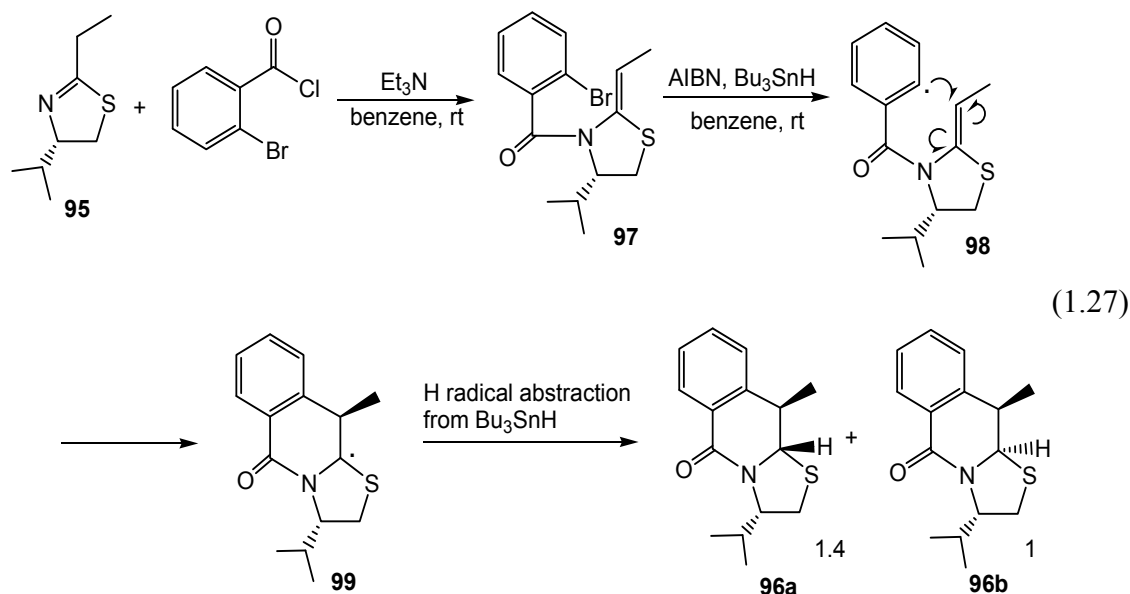
Benzoylation of the cyclic ketene-*N,O*-acetal 3,4,4-trimethyl-2-methylene-oxazolidine (**27**), in presence of triethylamine, gave rise to β -keto cyclic ketene-*N,O*-acetal **90** (Equation 1.25).¹⁹ The β -carbon attacks the carbonyl carbon of the acid chloride, followed by loss of chloride to give the corresponding oxazolidinium cation **91**. This ion is deprotonated by triethylamine at the β -carbon, forming **90**. Cyclic ketene-*N,S*-acetals react with aroyl chlorides in a similar manner.¹⁹



Benzoylation of 2-methyl-2-thiazoline (**92**), in the presence of triethylamine, went through *N*-benzoylated cyclic ketene-*N,S*-acetal intermediate **93** to give *N,C*-dibenzoylated cyclic ketene-*N,S*-acetal **94** (Equation 1.26).^{19,20} The β -benzoyl group lies *trans* to the ring nitrogen to avoid steric interactions of the two benzoyl groups. 2,4,4-Trimethyl-2-oxazoline reacted with benzoyl chloride in a similar manner.¹⁹

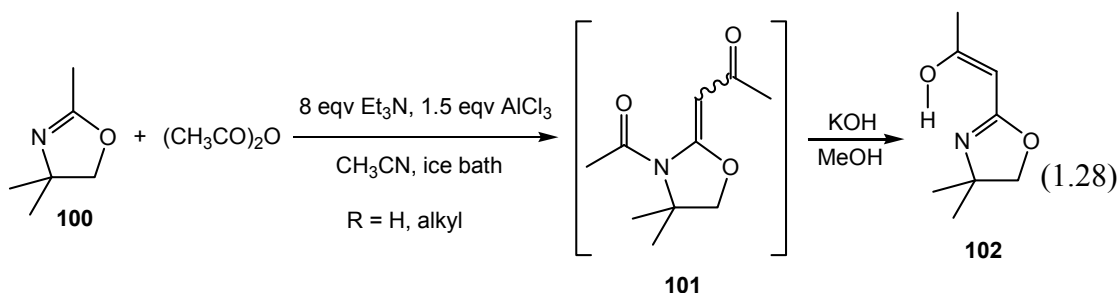


The *N*-benzoylated cyclic ketene-*N,S*-acetal intermediate **93** can be intercepted intramolecularly on certain occasions. For example, *N*-benzoylation of optically active 2-ethyl-4-isopropyl-1,3-thiazoline (**95**) by 2-bromobenzoyl chloride, followed by intramolecular radical cyclization, gave the fused-ring compound 3-isopropyl-10-methyl-2,3,10,10a-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one (**96a-b**) as two stereoisomers (Equation 1.27).^{21a} The aryl radical **98** attacked the exocyclic double bond *cis* to the C-4 isopropyl group to form **99** (attack *trans* to the C-4 isopropyl group was not found), and the hydrogen abstraction by radical **99** from Bu₃SnH occurred both *cis* and *trans* to the C-4 isopropyl function. Thus, only two stereoisomers **96a** and **96b** were isolated rather than four. The ratio of the two stereoisomers **96a** and **96b** was thought to be controlled by the stereochemistry at both C-4 and the β-carbon. 2-Methyl-2-oxazolines underwent this type of radical cyclization in a similar manner.^{21b}

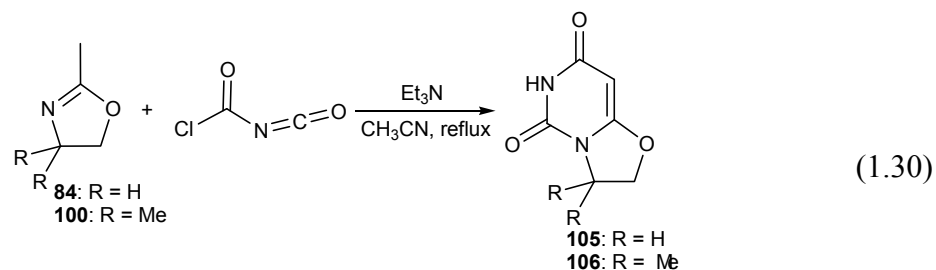
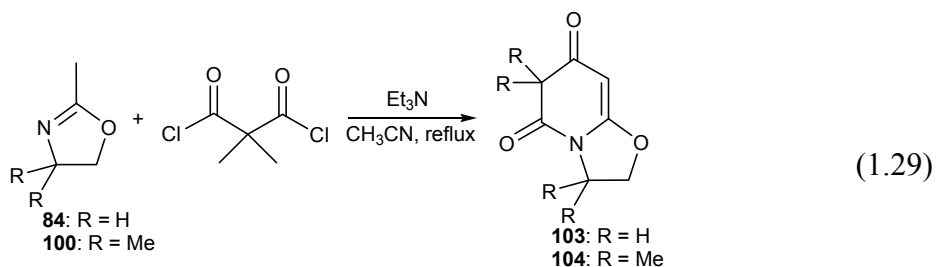


Acylation of 2-methyl-2-oxazoline **100** with enolizable aliphatic acid chlorides was not successful when triethylamine was used as the acid scavenger.^{14e,19} Ketene

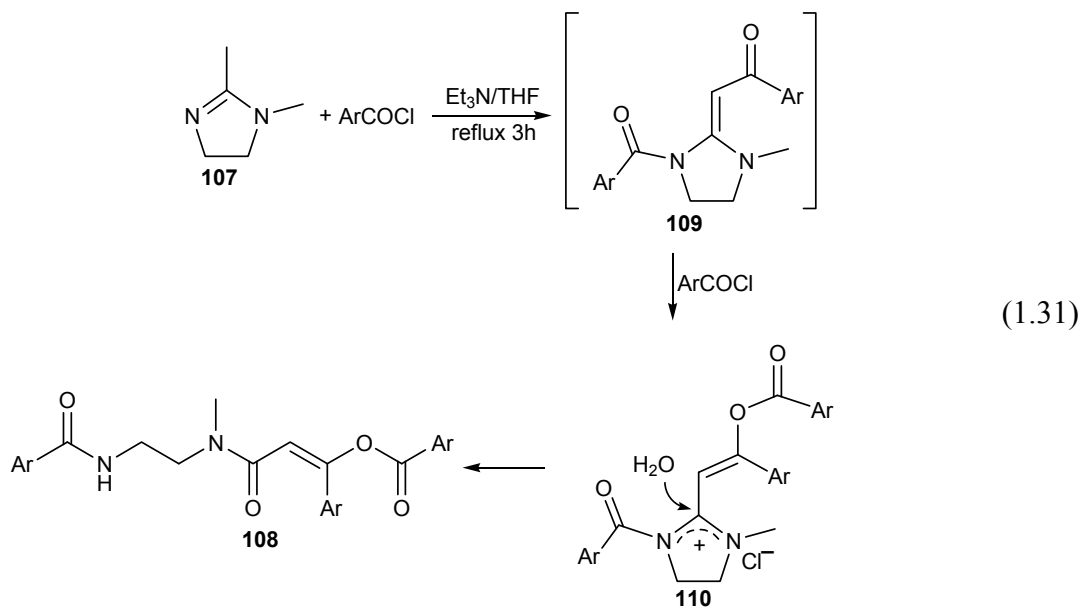
formation from these enolizable acid chlorides and triethylamine likely caused multiple complex reactions within the reaction system. For example, [2 + 2] cycloadditions with compounds bearing a double bond (C=C, C=X or N=X, where X=O, N, or S), or reactions with active olefins such as vinyl ethers, vinyl esters, enamines may have occurred.²² When acetic anhydride was used as the acetylating reagent with a stoichiometric amount of AlCl₃ and a large excess of triethylamine, the *N,C*-diacetylation product **101** was presumably achieved but not isolated. Instead, *N*-deacylation of **101** intermediate with KOH gave **102** (Equation 1.28).²³



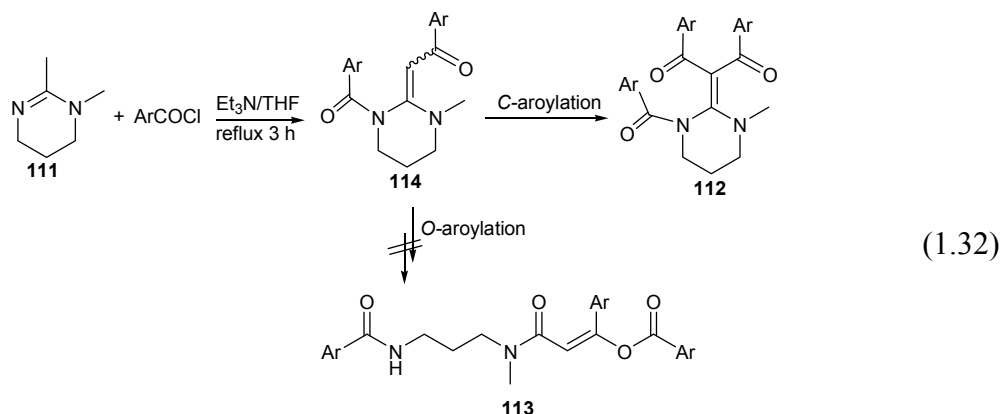
Acylation of 2-methyl-2-oxazolines and 2-methyl-2-thiazoline with 1,3-dielectrophiles was also explored. *N,C*-Diacylation of 2-methyl-2-oxazolines **84** and **100** by nonenolizable 1,3-diacid chlorides generated fused ring heterocycles **103** and **104** (Equation 1.29).²⁴ The β-keto function was formed *cis* to the ring nitrogen, in contrast to the case where a monoacid chloride was used as the acylating reagent (see Equation 1.26). Another bis-electrophile, *N*-(chlorocarbonyl) isocyanate, reacted with 2-methyl-2-oxazolines **84** and **100** the same way to give **105-106** (Equation 1.30). 2-Methyl-2-thiazoline reacted in a similar manner with 1,3-diacid chlorides or *N*-(chlorocarbonyl) isocyanate.²⁴



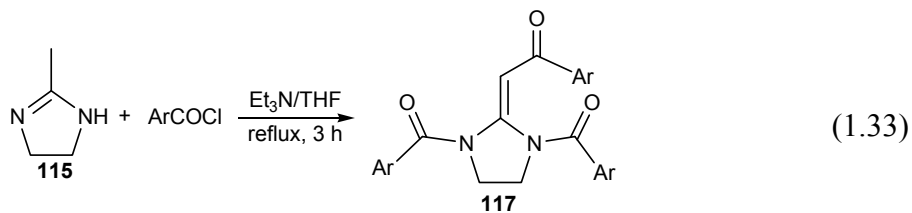
Aroylation of 1,2-dimethyl-4,5-dihydroimidazole **107** followed by hydrolysis during workup, gave ring-opened product **108** (Equation 1.31).²⁵ This reaction probably went through *N,C*-diaroylation intermediate **109**. *O*-Aroylation of the β -keto function followed by H_2O nucleophilic attack on C-2 of the resulting imidazolium ion **110**, led to ring-opening via the N-C bond breaking. *O*-Aroylation occurs due to the electron donation from the two nitrogens, which makes the β -keto oxygen electron rich.



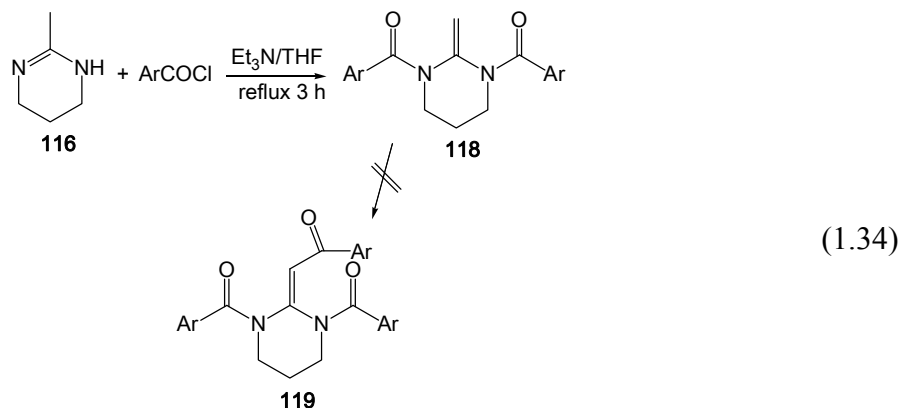
In contrast, aroylation of 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine (**111**) gave ring-retained *N,C,C*-triarylation product, 2-(1-benzoyl-3-methyl-tetrahydro-pyrimidin-2-ylidene)-1,3-diphenylpropane-1,3-dione (**112**) (Equation 1.32).²⁶ Ring-opened product **113**, analogous to **108**, was not formed because the β -carbon of the *N,C*-bisarylation intermediate **114** maintained sufficient nucleophilicity to react with aroyl chlorides faster than the β -keto oxygen.



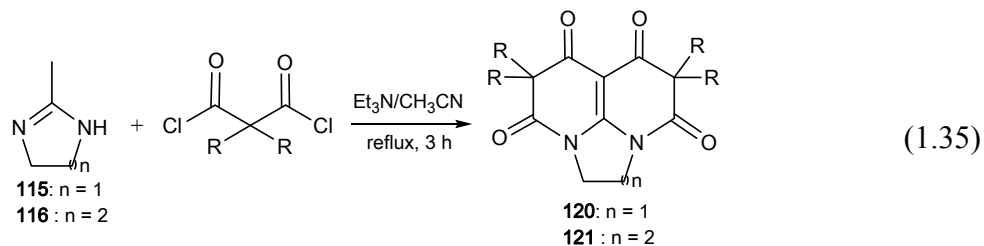
When the *N*-methyl group of **107** or **111** is replaced by a hydrogen, the resulting 2-methyl imidazoline (**115**) or 2-methyl-1,4,5,6-tetrahydropyrimidine (**116**) has one additional nucleophilic site, the NH site. Aroylation of **115** gave the *N,N,C*-triarylation product **117** (Equation 1.33).²⁶



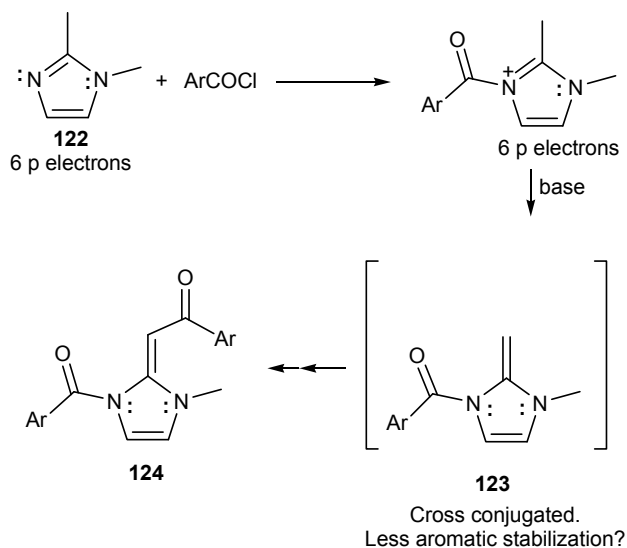
In contrast, **116** underwent *N,N*-diarylation to form **118** (Equation 1.34).²⁶ The expected triarylated product **119** was not obtained.



2-Methyl imidazoline (**115**) and 2-methyl-1,4,5,6-tetrahydropyrimidine (**116**) underwent double *N,C*-diacylations with two equivalent α,α -disubstituted malonoyl dichlorides leading to fused three ring systems **120** and **121**, respectively (Equation 1.35).²⁷

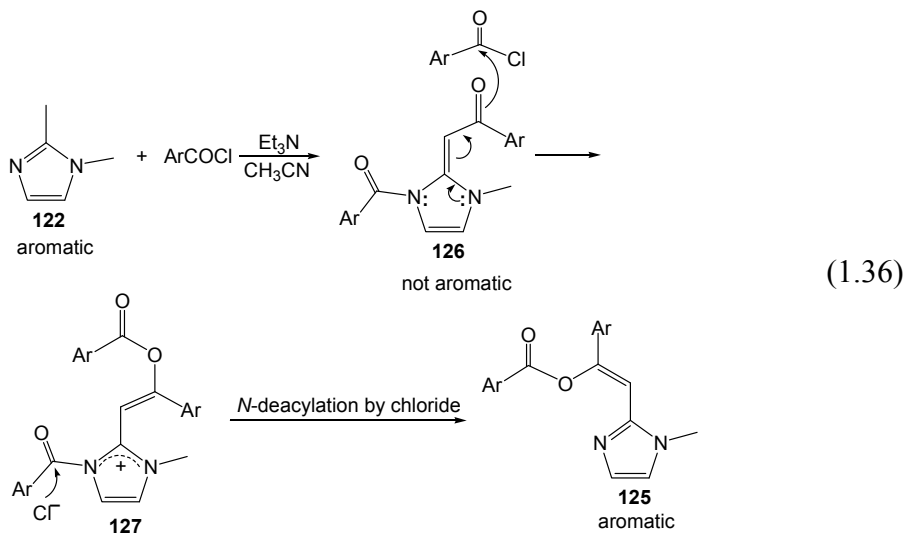


It was of interest to see if the benzoylation chemistry displayed by 2-methylimidazolines finds analogy in their aromatic imidazole analog **122**. If the same chemistry occurs, formation of a cross conjugated system is involved which presumably has less aromatic stabilization than **122** (Scheme 1.2).



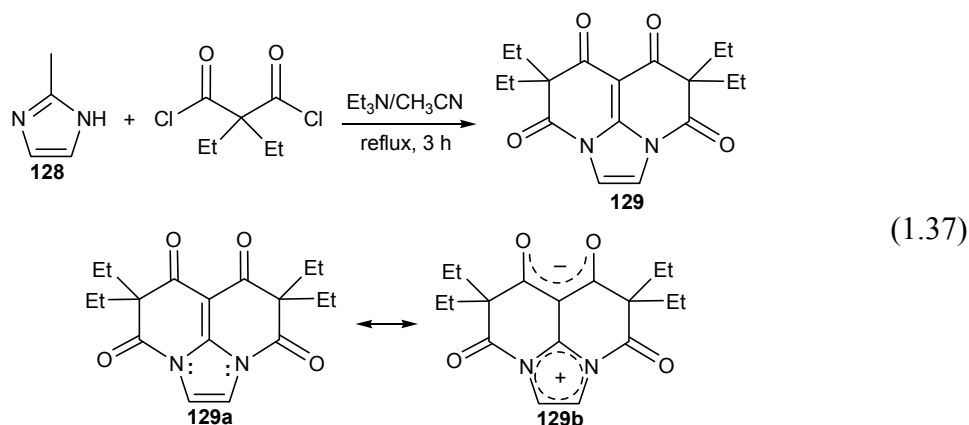
Scheme 1.2 Possible aroylation of 1,2-dimethyl-2-imidazole

Aroylation of 1,2-dimethyl-2-imidazole (**122**), however, led to *C,O*-diaroylation product **125**, and not **124** shown in Scheme 1.2.²⁸ This could have occurred via aroylation of *N,C*-diaroylation product **126** to give *N,C,O*-triaroylation product **127** followed by *N*-dearoylation by chloride anion (Equation 1.36).

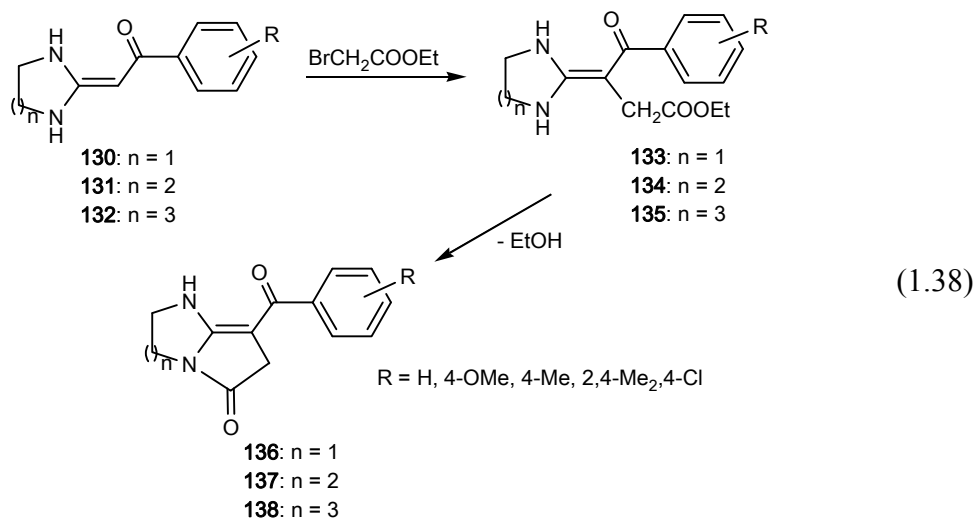


Acylation of 2-methylimidazole (**128**) with α,α -disubstituted malonoyl dichloride gave double *N,C*-diacylation adduct **129**, similar to its saturated analogs (Equation

1.37).²⁹ The exocyclic carbon-carbon double bond of **129** is highly polarized. In addition to the strong “push-pull” effect, the contribution of the hybrid **129b** may be favored if its aromatic stabilization is enhanced.

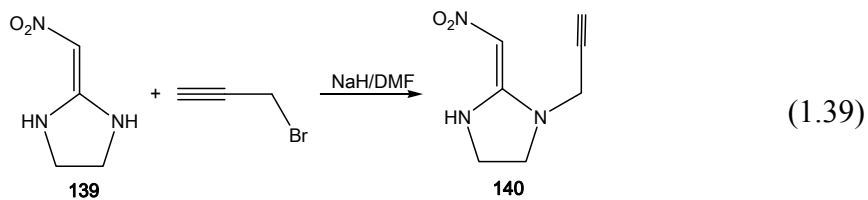


Alkylation of cyclic ketene-*N,N*-acetals **130-132** with ethyl bromoacetate, under neutral conditions, gave *C*-alkylated products **133-135**. This is followed by *N*-nucleophilic addition-elimination to afford γ -lactam-fused heterocycles **136-138** (Equation 1.38).³⁰ Benzyl chloride reacted with **130-132** to also give *C*-alkylation.³⁰

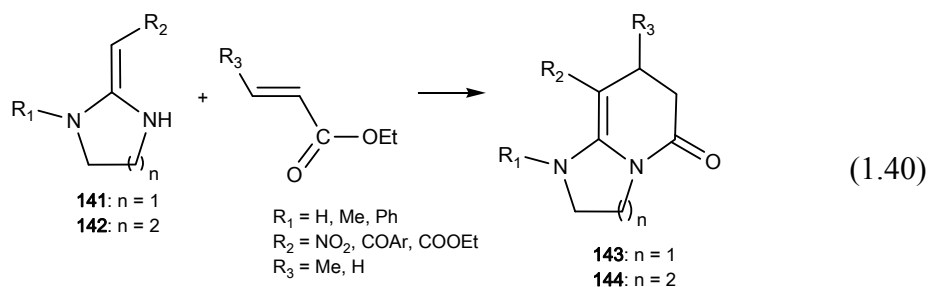


In contrast, β -nitro cyclic ketene-*N,N*-acetal **139** reacted with propargyl bromide, in the presence of sodium hydride, to afford *N*-alkylated compound **140** exclusively

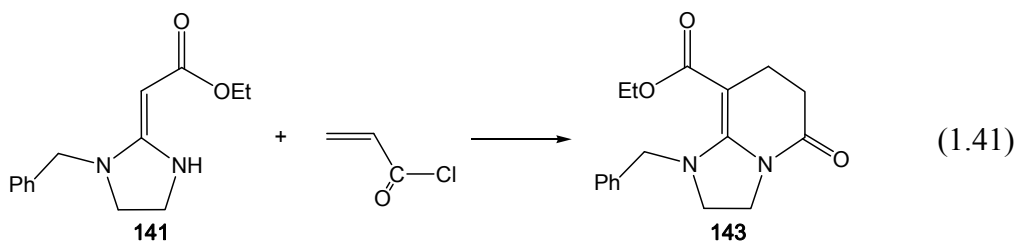
(Equation 1.39).³¹ The nitro group reduces the β -carbon nucleophilicity such that *N*-alkylation rather than *C*-alkylation occurred.



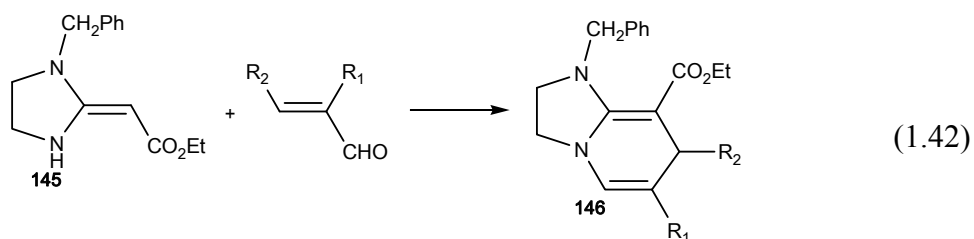
Reactions of β -substituted cyclic ketene-*N,N*-acetals **141,142** with α,β -unsaturated esters³² give fused compounds **143,144** through Michael addition and *N*-nucleophilic addition (Equation 1.40).



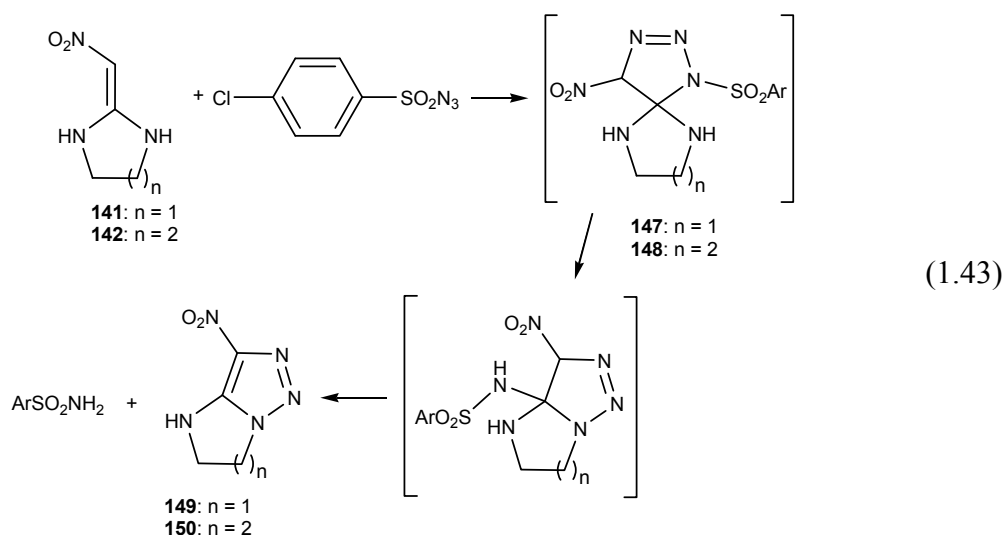
Reaction of β -substituted cyclic ketene-*N,N*-acetal **141** with propenoyl chloride³³ give fused compound **143** through *N*-acylation followed by β -*C*-Michael addition (Equation 1.41).

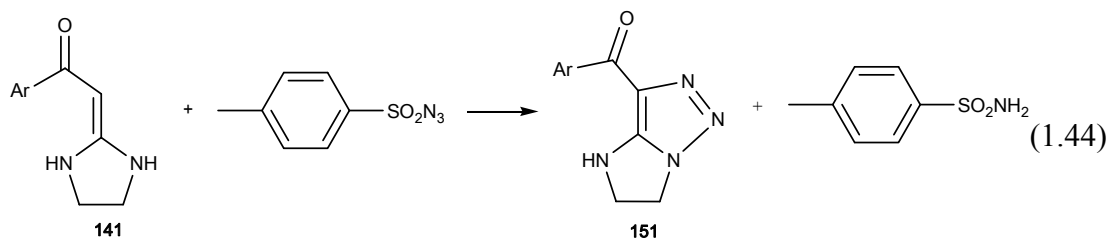


Reactions of cyclic ketene-*N,N*-acetal **145** with α,β -unsaturated aldehydes afforded fused 1,4-dihydropyridine compounds **146** through Michael addition followed by *N*-nucleophilic addition and intramolecular dehydration (Equation 1.42).³⁴

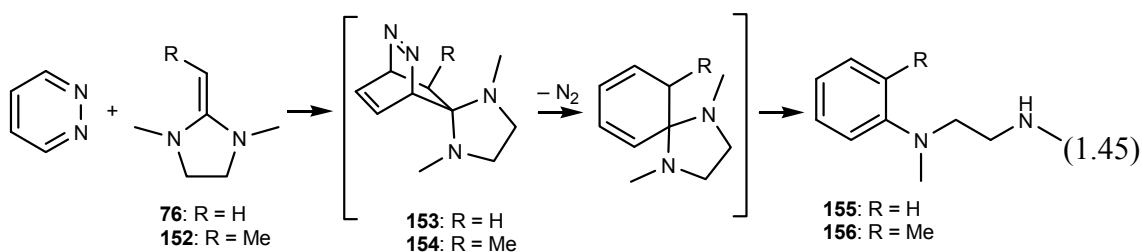


Aside from the β -carbon nucleophilic additions demonstrated above, cyclic ketene-*N,N*-acetals also undergo 1,3-dipolar additions via their polarized exocyclic carbon-carbon double bonds. The electron rich terminal methylene group adds to the positive end of a 1,3-dipole, and the C-2 adds to the negative end. For example, β -nitro cyclic ketene-*N,N*-acetals **141-142** reacted with *p*-chlorobenzenesulphonyl azide to give 1,3-dipolar cycloadducts **147-148** as intermediates, followed by a Dimroth rearrangement and deamination to give **149-150** (Equation 1.43).³⁵ β -Keto cyclic ketene-*N,N*-acetal **141** reacted with *p*-methylbenzenesulfonyl azide giving a similar product **151** (Equation 1.44).³⁶

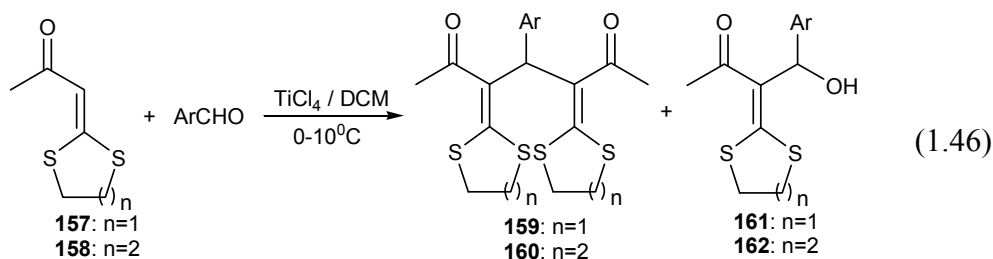




Electron rich β -keto cyclic ketene-*N,N*-acetal **76,152** underwent an inverse demand Diels-Alder reaction with the electron poor diene, pyridazine, to form 1,4-adduct **153-154** as an intermediate. The latter lost a nitrogen molecule and rearranged to form diamine **155-156** (Equation 1.45).³⁷

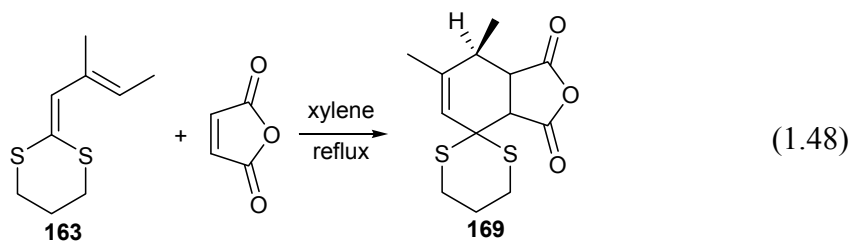
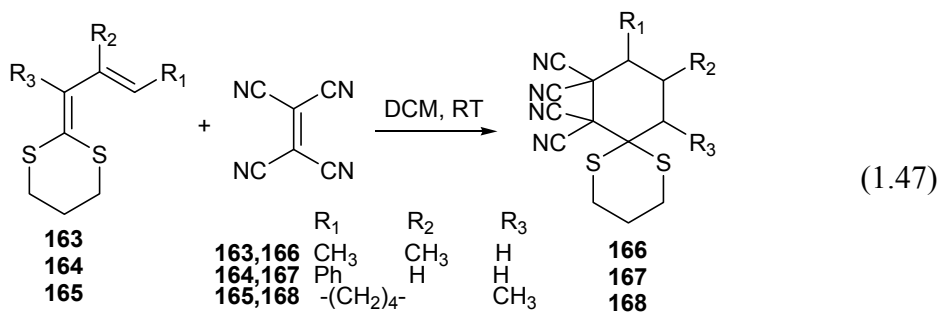


β -Keto cyclic ketene-*S,S*-acetals **157-158** underwent Baylis-Hillman reactions with arylaldehydes carrying electron-withdrawing groups to give **159-160** and **161-162**, mediated by stoichiometric amounts of TiCl_4 (Equation 1.46).³⁸ This reaction didn't occur using the typical bases for Baylis-Hillman reactions such as 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicycloundec-7-ene or triethylamine.

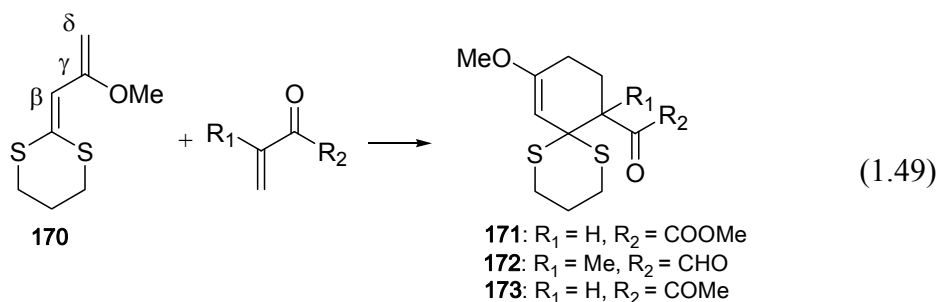


β -Vinyl substituted cyclic ketene-*S,S*-acetals **163-165** are electron rich 1,3-dienes.³⁹ They react with electron poor tetracyanoethylene to form **166-168** (Equation 1.47). The activation effect of the two thioalkoxy substituents overrode any buildup of a

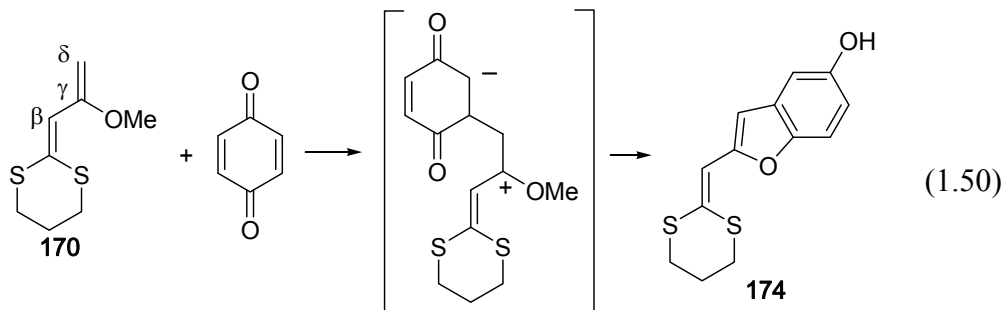
steric hindrance in this reaction. With less reactive maleic anhydride, however, only cyclic ketene-*S,S*-acetal **163** reacted to form a Diels-Alder adduct **169** (Equation 1.48). Less reactive dienophiles such as diethyl maleate, diphenylacetylene, and *p*-benzoquinone did not react.



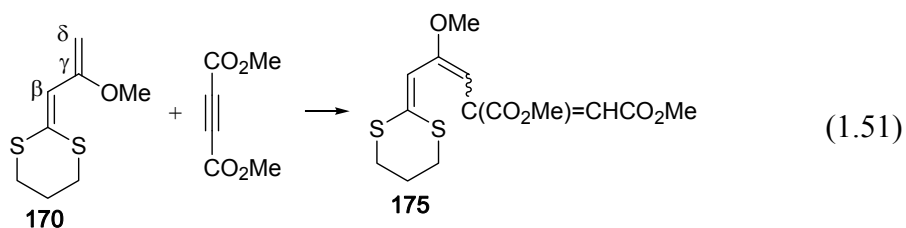
When an electron donating methoxy group is introduced to the γ position of a vinyl cyclic ketene acetal, the resulting diene is similar to a Danishefsky's diene. For example, diene **170** is more electron rich and participated in Diels-Alder reactions with less reactive electrophiles such as methyl vinyl ketone, methacrolein, and methyl acrylate to give adducts **171-173** (Equation 1.49).⁴⁰



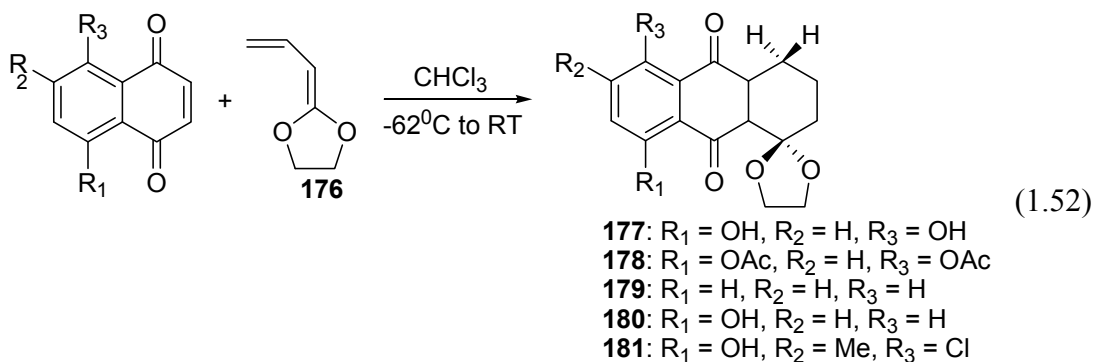
Cyclic ketene-*S,S*-acetal **170** reacted with strong electrophiles such as 1,4-benzoquinone, giving rise to compound **174** (Equation 1.50)⁴⁰. This reaction possibly went through a Michael addition of **170** via its δ -carbon to 1,4-benzoquinone followed by cyclization, with elimination of methanol, and tautomerization in unspecified order. Such a sequence finds analogy in the reaction of ketene acetals with quinones.



Cyclic ketene-*S,S*-acetal **170** reacted with dimethyl acetylenedicarboxylate giving rise to Michael adduct **175** (Equation 1.51) in a similar manner.⁴⁰



Cyclic ketene-*O,O*-acetal **176** reacted as an electron rich diene with naphthoquinones to give Diels-Alder adducts **177-181** (Equation 1.52).⁴¹



In conclusion, cyclic ketene acetals display multiple reaction patterns depending on identity of the heteroatoms (O,O, N,N, N,O, N,S, etc.), ring sizes, substituents on the ring and on the β -carbon. This rich chemistry offers abundant synthetic possibilities. Yet many uncertainties about how these changes lead to diverse reactivities remain to be addressed. Also, it has often been difficult to predict what reactions will occur using cyclic ketene acetal reagents.

Much work has been done on cyclic ketene-*O,O*-, and -*N,O*-acetal polymerizations. Nucleophilic reactions of cyclic ketene-*O,O*- and -*N,N*-acetals with electrophiles were also extensively explored. A few Diels-Alder reactions between electron rich β -vinyl substituted cyclic ketene-*S,S*- or -*O,O*-acetals with electron poor dienophiles have been reported, but inverse demand Diels-Alder reactions between electron rich cyclic ketene acetals and electron poor dienes are rarely explored. Reactions between cyclic ketene acetals and electrophiles often result in cyclic ketene acetal polymerizations, not the desired nucleophilic substitutions.

Little work has been published on reactions of cyclic ketene-*N,O*-acetals with various electrophiles. *N*-methyl cyclic ketene-*N,O*-acetals studied previously were invariably generated in advance from 2-alkyl-2-oxazolines or 2-alkyl-2-oxazines via *N*-methylation by methyl iodide followed by deprotonation with sodium hydride. This multistep sequence is quite inefficient and inconvenient because of the highly water sensitive nature of cyclic ketene-*N,O*-acetals. Transformations of cyclic ketene-*N,O*-acetals to other heterocycles have not been reported.

This dissertation will focus on *in situ* generation of *N*-methyl-cyclic ketene-*N,O*-acetals and their reactions with various electrophiles. Acylation of 2-methyl-2-oxazolines

and 2-methyl-2-oxazine to generate *N*-acyl-cyclic ketene-*N,O*-acetals will be extended beyond using acid chlorides. More push-pull and possibly zwitterionic structures derived from cyclic ketene-*N,O*-acetals are likely to be synthesized with the possible discovery of new reactions. This work is a continuation of Pittman group's work on cyclic ketene acetal chemistry and its synthetic potential. In this study, no intention exists to design the synthesis of specific natural products via cyclic ketene-*N,O*-acetal chemistry. Instead, the intent is to simply expand the scope of reaction chemistry to further understand cyclic ketene acetal behavior.

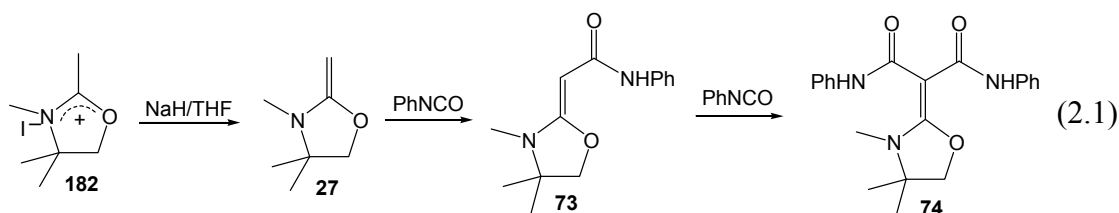
CHAPTER II

IODIDE-CATALYZED REARRANGEMENT OF β,β -DI(*N*-ARYLAMIDO)

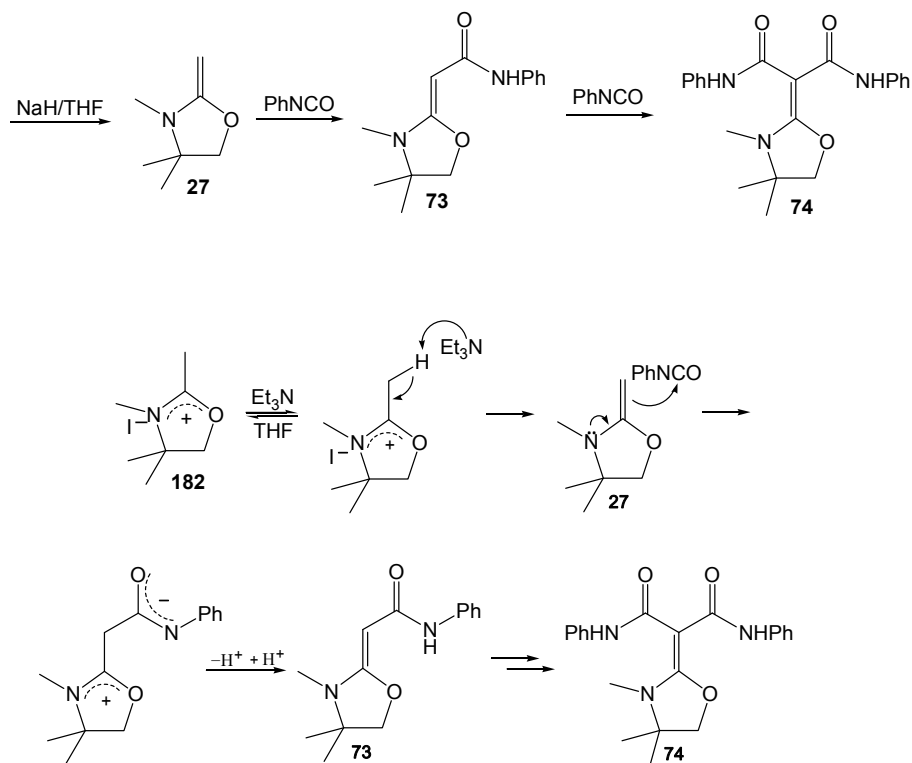
CYCLIC KETENE-*N,O*-ACETALS

Introduction

Cyclic ketene-*N,O*-acetal **27** reacted with phenyl isocyanate to give β -mono (*N*-phenylamido) cyclic ketene-*N,O*-acetal **73** or β,β -bis (*N*-phenylamido) cyclic ketene-*N,O*-acetal **74** (Equation 2.1).¹⁴ In these reactions, **27** was generated in advance by reacting 2,3,4,4-tetramethyl-2-oxazolinium iodide (**182**) with sodium hydride. One of the acidic 2-methyl protons of **182**, activated by the neighboring iminium group, was quantitatively removed by NaH to form **27**. Purification of **27** by distillation followed by its reaction with phenyl isocyanate generated **73** or **74**.



The 2-methyl group of **182** may also be reversibly deprotonated by triethylamine.⁴² Therefore, if **182**, triethylamine and phenyl isocyanate are reacted in one pot, cyclic ketene-*N,O*-acetal **27** will likely be generated *in situ* from **182** and triethylamine. If **27** reacts further with the isocyanate to form **73** or **74**, a one pot process would result. A mechanism that could account for this substitution reaction is shown in Scheme 2.1.



Scheme 2.1 Reaction of cyclic ketene-*N,O*-acetal **27**, generated *in situ* from 2,3,4,4-tetramethyl-2-oxazolinium iodide (**182**) and triethylamine, and phenyl isocyanate.

One pot reactions of aryl isocyanates were investigated with cyclic ketene-*N,O*-acetal **27**, generated *in situ* from **182** and triethylamine, and cyclic ketene-*N,O*-acetal **56**, generated *in situ* from 2,3-dimethyl-2-oxazolinium iodide **190** and triethylamine. One pot reactions of benzoyl chloride with *in situ* generated cyclic ketene-*N,O*-acetal **27** were also attempted. Results are reported below.

Results and discussion

2,3,4,4-Tetramethyl-2-oxazolinium iodide (**182**) and 2,3-dimethyl-2-oxazolinium iodide (**190**) were easily prepared from commercially available 2,4,4-trimethyl-2-oxazoline and 2-methyl-2-oxazoline, respectively, and methyl iodide. They were used for

in situ generation of cyclic ketene-*N,O*-acetals. Eight substituted phenyl isocyanates with a broad range of substituents (including electron withdrawing and electron donating groups) were employed to explore how electronic factors affect reactions. Results of reactions of aryl isocyanates with cyclic ketene-*N,O*-acetals **27** (Equation 2.2) and **56** (Equation 2.3) are summarized in Tables 1 and 2, respectively.

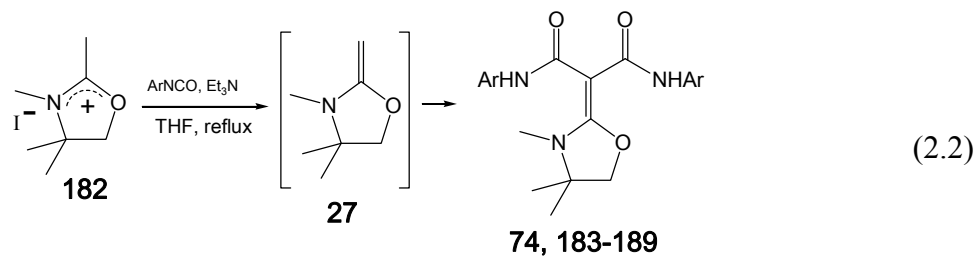
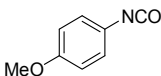
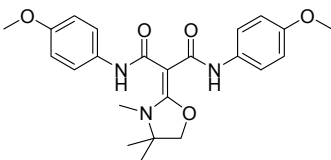
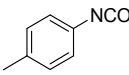
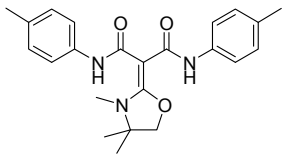
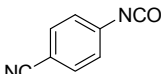
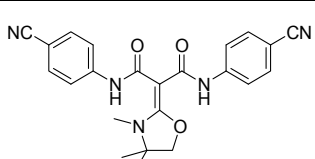
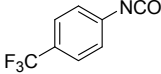
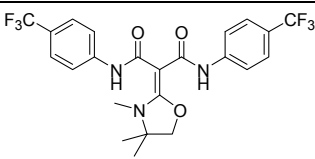
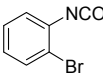
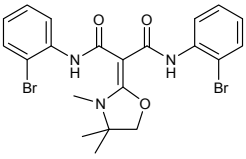


Table 2.1 Reactions of *in situ* generated cyclic ketene-*N,O*-acetal **27** with isocyanates^a

Entry	Isocyanate	Product	Yield ^b (%)
1			79
2			76
3			76

Table 2.1 (Continued)

Entry	Isocyanate	Product	Yield ^b (%)
4		 185	64
5		 186	69
6		 187	36
7		 188	82
8		 189	76

^a Reactions were run in refluxing THF for 5 h. Reactant molar ratio **182**:Et₃N:isocyanate = 1:1.3~1.5:2.2~2.3. Column chromatography (stationary phase: silica gel, eluting solvent: acetone/hexanes or ethyl acetate/hexanes) was used for purification.

^b Isolated yield

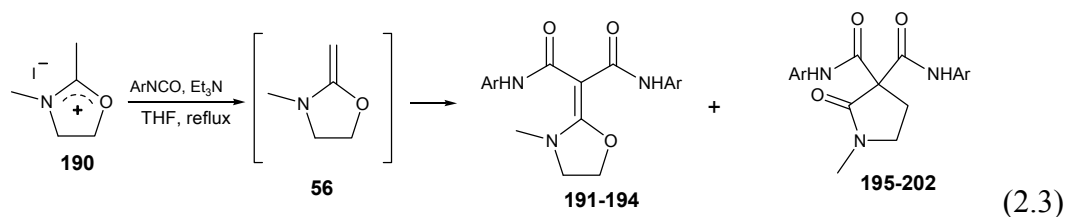


Table 2.2 Reactions of *in situ* generated cyclic ketene-*N,O*-acetal **56** with isocyanates^a

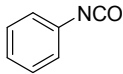
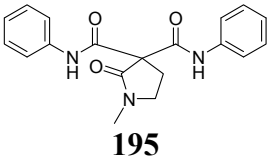
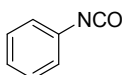
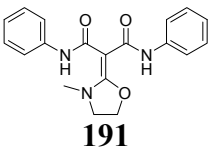
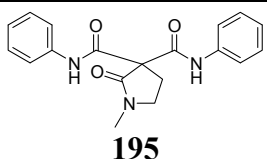
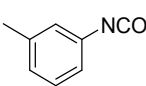
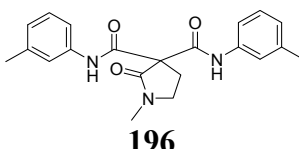
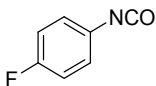
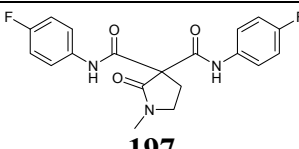
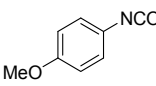
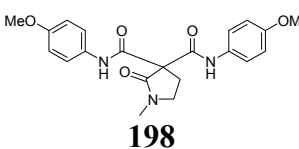
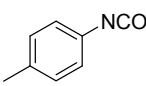
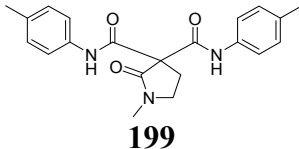
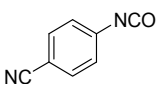
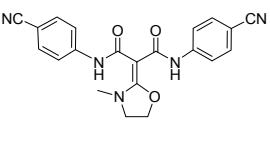
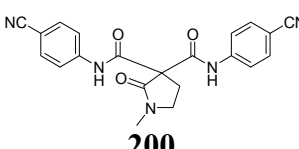
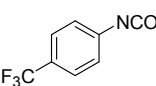
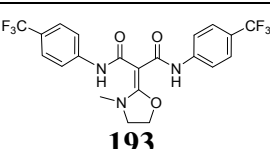
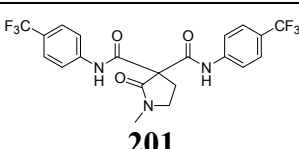
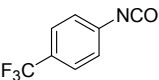
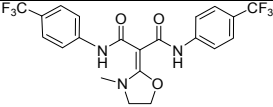
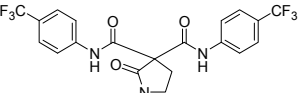
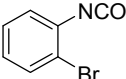
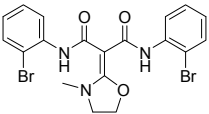
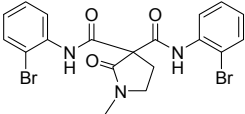
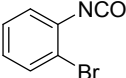
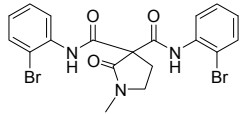
Entry	Isocyanate	191-194	Yield ^b (%)	195-202	Yield ^b (%)
1 ^c		none		 195	39
2 ^d		 191	55	 195	trace
3		none		 196	73
4		none		 197	85
5		none		 198	62
6		none		 199	67
7		 192	5	 200	28
8		 193	14	 201	69

Table 2.2 (Continued)

Entry	Isocyanate	191-194	Yield ^b (%)	195-202	Yield ^b (%)
9 ^e			5		75
10			29		42
11 ^f		none			68

^a Reactions were run in refluxing THF for 5 h. Reactant molar ratio **190**:Et₃N:isocyanate = 1:1.3~1.5:2.2~2.3. Column chromatography (stationary phase: silica gel, eluting solvent: acetone/hexanes or ethyl acetate/hexanes) was used for purification.

^b Isolated yield

^c Reactant molar ratio: **190**:Et₃N:isocyanate = 1:1.3:1.1.

^d Reaction was run in THF at room temperature where rearrangement to lactam is exceedingly slow. The product was purified by recrystallization from DCM.

^e Reaction was run in refluxing THF for 13.5 h.

^f Reaction was run in refluxing anhydrous 1,4-dioxane for 11.5 h

This reaction sequence generated β,β -bis(*N*-arylamido) cyclic ketene-*N,O*-acetal **74** nicely in refluxing THF 5 h where two methyl substituents are on C-4 (Table 2.1, Entries 1-8). However, when C-4 has two hydrogen substituents, refluxing in THF 5 h did not give the corresponding β,β -bis(*N*-arylamido) cyclic ketene-*N,O*-acetals (Table 2.2, Entries 1, 3, 4, 5, 6) or only gave them in low yields (Table 2.2, Entries 7, 8, 10). Unexpectedly, rearranged lactam products **195-202** (Table 2.2, Entries 1, 3, 4, 5, 6, 7, 8, 10) resulted when cyclic ketene-*N,O*-acetal **56** without methyl substituents on C-4 was used. The FTIR spectrum of **195** (Ar = Ph) exhibited a characteristic tertiary amide carbonyl stretching band⁴³ at 1696 cm⁻¹. This was characteristic of all the lactams **195-202**. The crystal structure of **195** is shown in Figure 2.1.

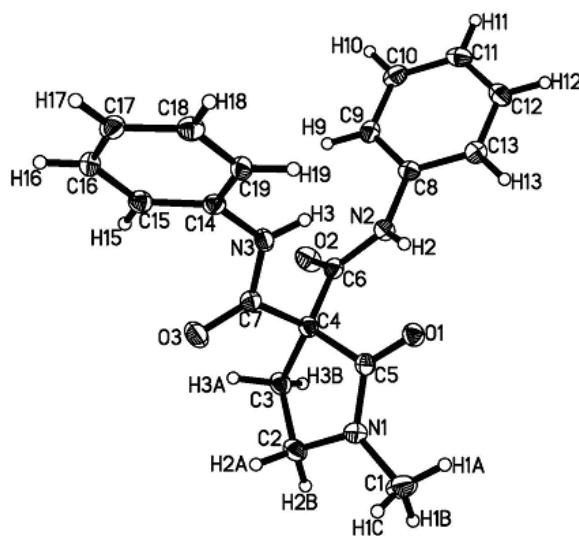


Figure 2.1 Crystal structure of α,α -bis(*N*-phenylamido)- γ -lactam **195**, CCDC: 794113

Rearrangement to lactam **195** did not readily occur at room temperature. Cyclic ketene-*N,O*-acetal **56** reacted with 2 equivalents of phenyl isocyanate (Table 2.2, Entry 2) to give β,β -bis(*N*-phenylamido) cyclic ketene-*N,O*-acetal **191** almost exclusively at room temperature in THF. Only trace amounts of the rearranged lactam **195** was detected by TLC. The structure of **191** was confirmed by X-ray crystallography (Figure 2.2).

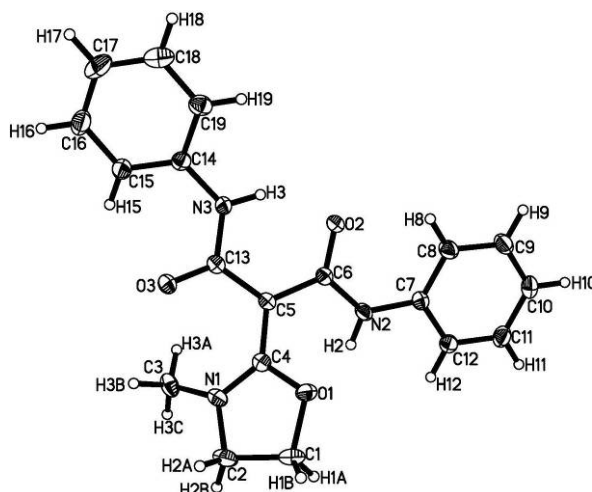
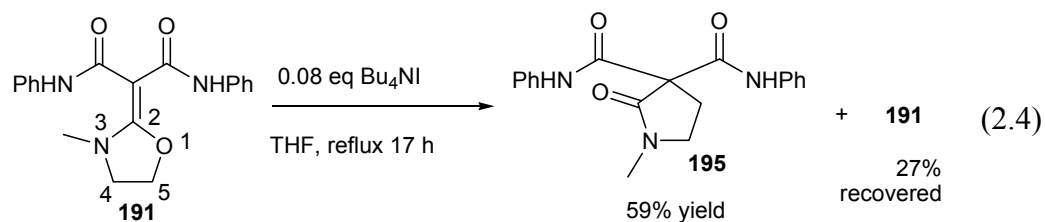


Figure 2.2 Crystal structure of 2-(3-methyloxazolidin-2-ylidene)-*N,N'*-diphenylmalonamide **191**. CCDC: 794114

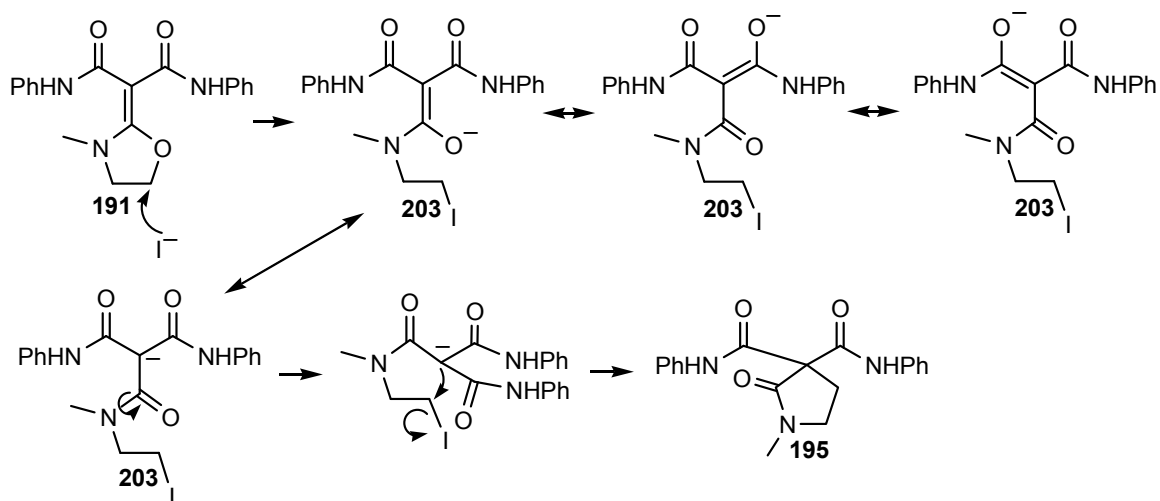
Somewhat slower rearrangement rates to lactams were found with aryl isocyanates carrying an electron withdrawing group on the phenyl ring (*p*-NC-PhNCO (Table 2.2, Entry 7) and *p*-CF₃PhNCO (Table 2.2, Entry 8)). Longer reaction times led to a higher rearrangement yields (*p*-CF₃PhNCO, Table 2.2, Entry 9). *o*-Br-PhNCO also gave incomplete rearrangement after 5 h refluxing in THF (Table 2.2, Entry 10). Using 1,4-dioxane, which has a higher boiling point (101 °C) than THF (66 °C) as the solvent, and longer reaction time drove the rearrangement of β,β-bis(*N*-*o*-bromophenyl amido) cyclic ketene-*N,O*-acetal **194** to the lactam **202** quantitatively (Table 2.2, Entry 11).

To see if this reaction is a pure thermal rearrangement, the β,β-bis(*N*-phenylamido) cyclic ketene-*N,O*-acetal **191** was refluxed in THF for 3 h, but **191** was recovered and no **195** formed. Thus, heating alone does not cause the rearrangement. Refluxing **191** in THF, in the presence of a catalytic amount (0.08 eq.) of

tetrabutylammonium iodide, generated the rearranged product **195** in 59 % yield after 17 h (Equation 2.4). Hence, this rearrangement is catalyzed by iodide.



A mechanism is proposed in Scheme 2.2. Iodide attacks C-4 of **191**. The C-5 of a five-membered cyclic ketene-*N,O*-acetal is susceptible to nucleophilic attack when the β -carbon is protonated by a Brønsted acid or coordinated to a Lewis acid so the cyclic ketene-*N,O*-acetal acquires significant 1,3-oxazolinium character.^{12,14,44a-b} It is likely that the presence of two electron withdrawing groups at the β -carbon may also effect a significant 1,3-oxazolinium character facilitating the nucleophilic attack at the C-5. Upon O-C bond breaking, the negative charge on the ring-opened anion **203** is distributed over three oxygens and the β -carbon. After bond rotation, the negatively charged β -carbon of **203** attacks the primary iodide-bearing carbon in an S_N2 reaction, displacing iodide and generating five-membered ring lactam structure **195**. This process is catalytic in iodide.



Scheme 2.2 Proposed mechanism for iodide-catalyzed rearrangement of 2-(3-methyloxazolidin-2-ylidene)-*N,N'*-diphenyl-malonamide (**191**)

It is not clear why reactions of *in situ* generated cyclic ketene-*N,O*-acetal **56** with aryl isocyanates (*p*-CF₃PhNCO and *p*-NC-PhNCO), both carrying an electron withdrawing group on the *para* position of the phenyl ring, gave rearrangement products slower than when phenyl isocyanate was the electrophile. It is not likely that the generation of β,β-bis(*N*-phenylamido) cyclic ketene-*N,O*-acetal intermediate is slower in these two cases because reactions of cyclic ketene-*N,O*-acetal **27** with *p*-CF₃PhNCO and *p*-NC-PhNCO didn't show a significant rate difference from that with phenyl isocyanate. Thus, it is likely that the rearrangement reaction to the lactam is influenced by the substituent effect. The rearrangement process involves two steps, the first step is the ring opening via iodide attack on C-5 of **191**, and the second step involves bond rotation and S_N2 attack by the partially negatively charged β-carbon of **203** on the primary iodide-bearing carbon. This displaces iodide and generates the five-membered ring lactam **195**. If we assume that the β-carbon gains a significant negative charge in the transition state

of the ring-opening step, then an electron withdrawing group will help to further distribute negative charge. For example, the *p*-cyano group on the phenyl ring reduces the electron density on the nitrogen of the amido moiety, therefore reducing that nitrogen's ability to conjugate with the carbonyl group (Figure 2.3). This makes the amido group, C(O)NHPh-*p*-CN more electron withdrawing (less donating) than C(O)NHPh, leading to less electron density at the β -carbon. Therefore, the transition state for ring-opening will become more stable, so the activation energy for this step will be lowered. Thus, the first step will become faster, even if only slightly, due to the long distance of the cyano groups from the β -carbon. On the other hand, less electron density at the β -carbon due to the presence of electron withdrawing groups also means slower nucleophilic attack of the β -carbon on the iodine-bearing carbon, leading to slower ring reclosing. The overall rearrangement rate might be reduced due to the presence of the electron withdrawing group. However, kinetic studies would need to be performed to address this question. This was not a goal of this dissertation.

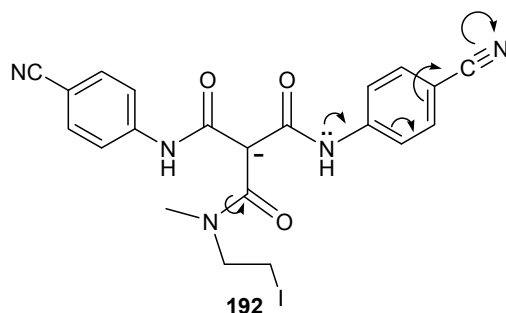


Figure 2.3 Electron withdrawing cyano groups reduce the electron density at the β -carbon

Compound **194** with an *o*-Br-Ph function also rearranged to the lactam **202** slowly, presumably due to steric factors.

The incoming iodide is sterically hindered from attacking C-5 (Figure 2.4) by the two methyl groups on C-4. The large iodide radius enhances this steric hindrance during nucleophilic attack on C-5. Thus, rearrangement in refluxing THF is not readily obtained.

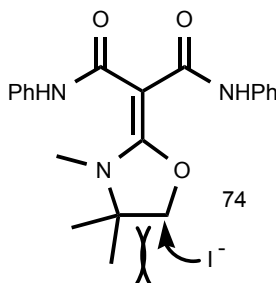
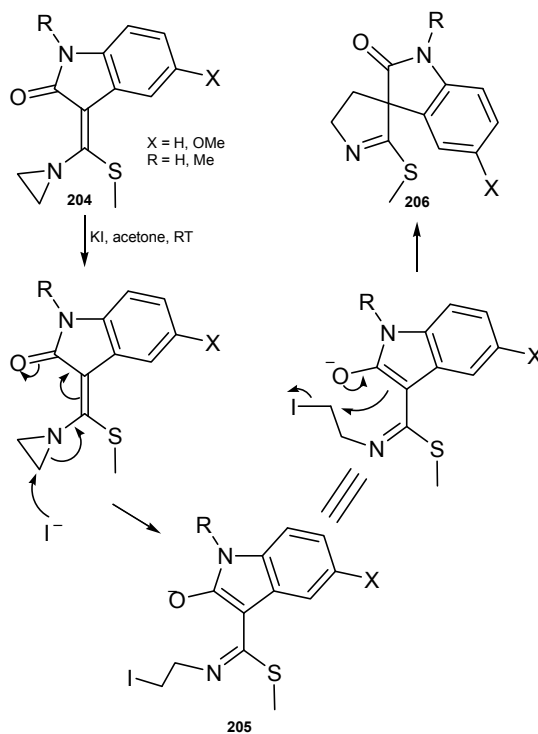


Figure 2.4 The 4,4-dimethyl groups prevent the iodide attack on C-5 of **74**

The formation of α,α -bis(*N*-arylamido) lactam **195** in the presence of only 1 equivalent of phenyl isocyanate occurs because cyclic ketene-*N,O*-acetal **56** was generated *in situ* from **190** during the reaction. Thus, excess phenyl isocyanate was present as **56** was formed. Under these conditions the second substitution occurred to form β,β -bis(*N*-phenylamido) cyclic ketene-*N,O*-acetal **191**, which rearranged to α,α -bis(*N*-phenylamido) lactam **195**.

This reaction is analogous to the iodide-induced rearrangement of [(*N*-aziridinomethylthio) methylene]-2-oxindoles (**204**) (Scheme 2.3).⁴⁵ The aziridine ring was susceptible to iodide attack to form an enolate intermediate **205**. This ambident anion attacked the carbon bearing iodine via its carbon end to furnish spiropyrrolidinyl-oxindoles **206**.



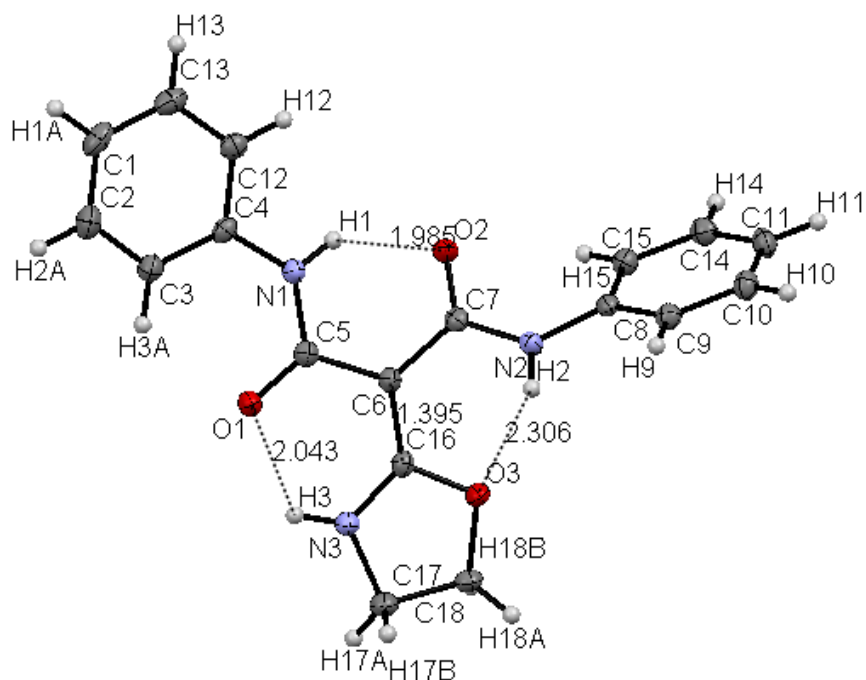
Scheme 2.3 Proposed mechanism for iodide-catalyzed rearrangement of [(*N*-aziridinomethylthio) methylene]-2-oxindoles (**204**)

191 was also subjected to refluxing in THF, in the presence of sodium bromide. However, no reaction was found based on TLC analysis of the products. Thus, bromide, unlike iodide, is not nucleophilic enough to open the ring. However, it is also possible that ring opening by bromide did occur but the β -carbon of the resulting anion may not be nucleophilic enough to displace bromide, which is a worse leaving group than iodide. This anion has no other way to further react but to reverse back to **191** by oxygen attack.

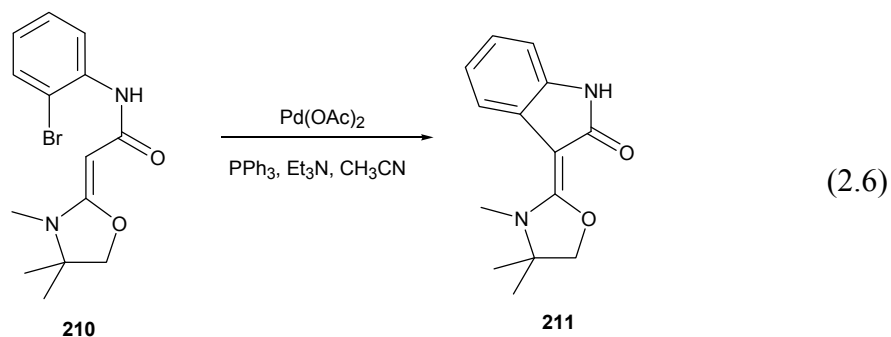
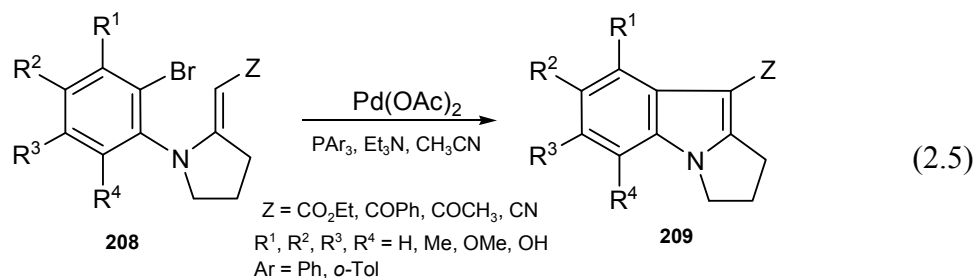
β,β -di(*N*-arylamido) cyclic ketene-*N,O*-acetals **74**, **183-189**, **191-202** have two magnetically equivalent amido functions, judged from the ^1H NMR and ^{13}C NMR. This is related to the elongated carbon-carbon double bond (1.419 Å for **191**) leading to a twisted solid state structure (twist angle^{46a-b} 36.54° for **191**, Table 2.3). In solution, rapid back-and-forth twisting (libration) of the plane defined by the two carbonyl carbons and

the β -carbon could be fast on the NMR time scale. Thus, these two functions would become indistinguishable by NMR. It is also possible that fast rotation about the elongated C-2 ring carbon to β -carbon bond occurs, equilibrating the amido groups on the NMR time scale. This would have a higher activation barrier than the libration (twisting) mentioned above.

By contrast, 2-oxazolidin-2-ylidene-*N,N'*-diphenyl-malonamide¹⁷ (**207**) showed non equivalent *N*-arylamido functions in its ¹H NMR. This big difference between **207** and **191**, which differ only by the substituent on the ring nitrogen (H for **207** and CH₃ for **191**), prompted us to examine the crystal structure of **207**, which is not reported in the literature. Thus, **207** was prepared from the reaction of 2-methyl-2-oxazoline **84** and phenyl isocyanate, following the procedure in the literature.¹⁷ The crystal structure of **207** indicated an intramolecular hydrogen bond between the ring NH function and the carbonyl oxygen of one of the *N*-arylamido functions (Figure 2.5, 2.043 Å). This locks that amido function to a fixed position, such that it is no longer equivalent to the other amido function. This hydrogen bond also hinders the librational motion of the C-5, C-6, C-7 plane with respect to the 5-membered ring's plane. This results in magnetically distinct amido groups. This contributes also to a small twist angle (3.18°) in the solid state.

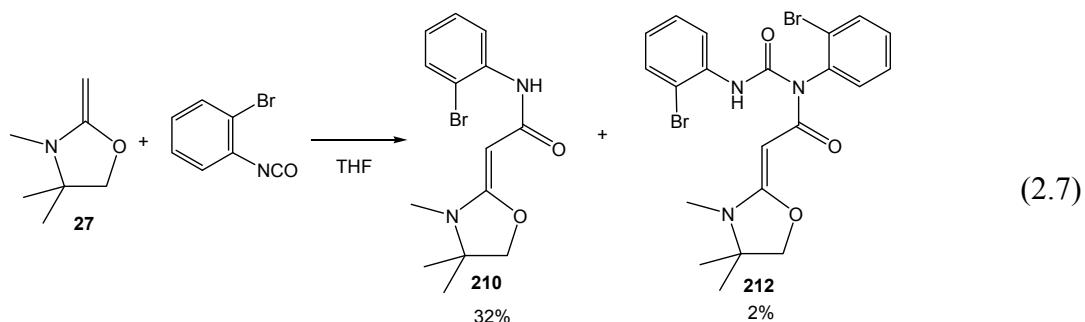


Several *N*-(2-bromoaryl) enaminones **208** were previously demonstrated to undergo intramolecular Heck reactions⁴⁷ to give pyrrolo[1,2*a*]indoles **209** (Equation 2.5). *N*-(2-Bromophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetamide (**210**), a five-membered β -(*N*-arylamido) cyclic ketene-*N,O*-acetal, contains an aryl bromide positioned such that an intramolecular Heck reaction could potentially connect the aryl carbon bearing the bromo substituent to the β -carbon of **210**. If successful, this reaction would provide a route to 3-(3,4,4-trimethyloxazolidin-2-ylidene)-1,3-dihydro-indol-2-one (**211**) which features two five-membered rings connected by the carbon-carbon double bond (see Equation 2.6).



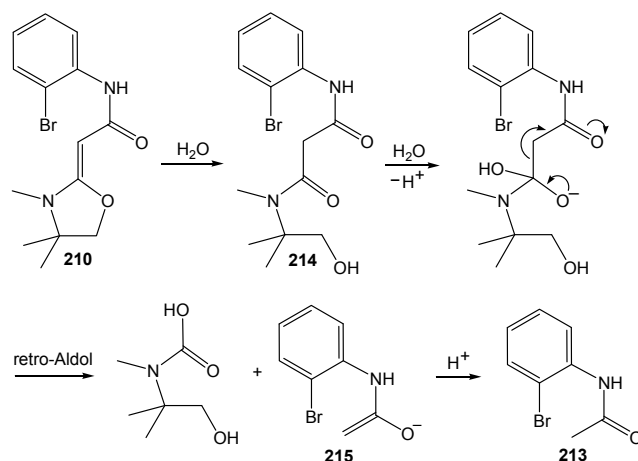
The synthesis of **210** involved the reaction of cyclic ketene-*N,O*-acetal **27**, generated in advance by the reaction of 2,3,4,4-tetramethyloxazolinium iodide (**182**) with sodium hydride, and the electrophile, 2-bromophenyl isocyanate (Equation 2.7).^{14e} However, **27** was not first purified by distillation. Instead, the **27**/THF solution was simply taken by a syringe for use in subsequent reactions. Monosubstitution occurred at

the β -carbon of **27** and **210** was isolated in 32 % yield. Compound **212**, arising from the nucleophilic addition of the β -amido nitrogen of **210** on 2-bromophenyl isocyanate, was also obtained in 2 % yield.



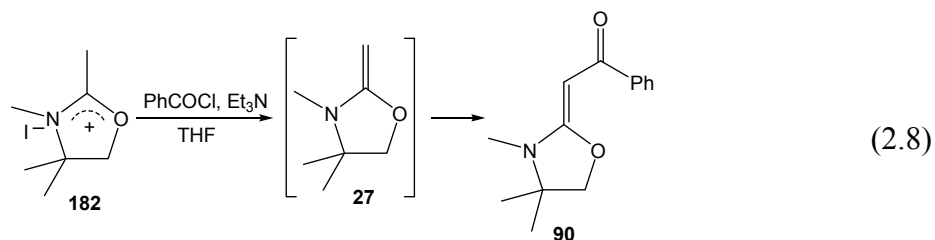
Having **210** in hand, the intramolecular Heck reaction was attempted (Equation 2.6). A mixture of *N*-(2-bromophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetamide (**210**) (0.275 g, 0.85 mmol, 1 eq.), palladium acetate (0.026 g, 0.11 mmol, 0.13 eq.), triphenyl phosphine (0.128 g, 0.48 mmol, 0.57 eq.) and triethylamine (0.202 g, 2.00 mmol, 2.35 eq.) was refluxed for 11.5 h in CaH₂ dried CH₃CN. Workup and purification gave two components, but the major one was unidentifiable by ¹H NMR. The minor component (white solid, 25 mg) was *N*-(2-bromophenyl)-acetamide (**213**), yield 14 %.

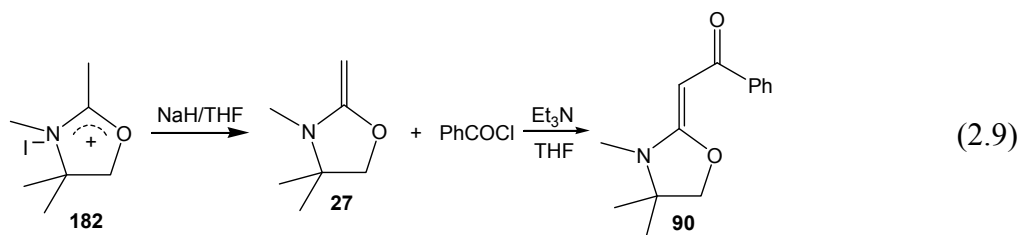
The formation of **213** could have resulted from hydrolysis of unreacted **210** during aqueous workup followed by a retro-Aldol reaction and protonation as illustrated in Scheme 2.4.



Scheme 2.4 A suggested mechanism for formation of *N*-(2-bromophenyl)-acetamide (**213**)

Success of the one pot reactions of aryl isocyanates with *in situ* generated cyclic ketene-*N,O*-acetal **27** prompted us to explore the feasibility of a similar one pot reaction of 2,3,4,4-tetramethyloxazolinium iodide (**182**), triethylamine and benzoyl chloride to generate 1-phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-ethanone (**90**) (Equation 2.8). Preparation of **90** was previously achieved^{14e,19} via a three-step sequence (Equation 2.9): reaction of **182** with sodium hydride to give 3,4,4-trimethyl-2-methylene-oxazolidine (**27**), distillation to isolate and purify **27** and then the reaction of **27** with benzoyl chloride to produce 1-phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-ethanone (**90**).





2,3,4,4-Tetramethyloxazolinium iodide (**182**) (1 eq.), triethylamine (2.23 eq.) and benzoyl chloride (1.06 eq.) were refluxed in one pot in anhydrous THF for 5 h. **90** was indeed generated in 35 % yield. This yield was also lower than the 49 % overall yield of the three step sequence.^{14e} However, the one pot procedure is more convenient, requiring less time and labor. Optimization of this sequence was not attempted.

In summary, the iodide-catalyzed β,β -bis(*N*-arylamido)-cyclic ketene-*N,O*-acetal rearrangement demonstrates both five-membered cyclic ketene-*N,O*-acetal ring opening by iodide nucleophilic attack on C-5 and ring reclosure via nucleophilic attack on C-5 by carbon of the resulting enolate intermediate, displacing iodide. Iodide catalysis plays a pivotal role in facilitating this cyclic ketene-*N,O*-acetal to lactam transformation because of iodide's unique dual nature. It is a good nucleophile as well as a good leaving group. This rearrangement is a good example how cyclic ketene-*N,O*-acetal chemistry can be employed in heterocycle synthesis. β,β -bis(*N*-arylamido)-cyclic ketene-*N,O*-acetals having two methyl substituents at C-4, however, did not rearrange due to hindrance of the iodide attack on C-5. This steric effect is pronounced and will show up repeatedly in the following chapters.

Experimental

Materials and Instruments

Melting points were recorded with a Mel-Temp apparatus and were uncorrected. The FT-IR spectra were recorded neat on a Thermo 18 Nicolet spectrometer using attenuated total reflection technique. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX-300 300 MHz spectrometer operating at 300 MHz for proton probing and 75 MHz for carbon probing. Chemical shifts were reported in ppm downfield from TMS, which was used as an internal standard. Splitting patterns are designed as “s, d, t, q and m”, which indicate “singlet, doublet, triplet, quartet and multiplet”, respectively. Bruker AXS Smart 1000, upgraded with APEX II detector and software which incorporates SHELX components,⁴⁸ was employed for crystal structure determination. All reactions were carried out under nitrogen. Tetrahydrofuran (THF) was distilled over Na/benzophenone under nitrogen. Triethylamine was distilled over calcium hydride under nitrogen. All other reagents were used as received. The silica gel used for the column chromatography was 70-230 mesh, pore size 60 Å (Aldrich). The above description also applies to materials and instruments involved in other chapters.

Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bisphenylamide (**195**)

2,3-Dimethyloxazolinium iodide (**190**) (3.50 g, 15.4 mmol, 1 eq.) was placed in a 100 mL flask, followed by dried THF (36 mL), Et₃N (1.96 g, 19.3 mmol, 1.25 eq.) and phenyl isocyanate (2.01 g, 16.5 mmol, 1.07 eq.). The suspension was refluxed for 5 h under nitrogen. Rotary evaporation was used to remove the solvent. Then

dichloromethane (23 mL) and saturated NaHCO₃ (30 mL) were added to the residue and the mixture was stirred for 10 min. The organic layer was washed with brine (2 x 24 mL), and dried over anhydrous Na₂SO₄. After concentrating by rotary evaporation, the crude product was purified by flash column chromatography over silica gel, using mixed ethyl acetate/hexanes as the eluting solvent. Upon solvent removal, 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bisphenylamide (**195**) was obtained (white solid, mp 114-115 °C. 2.02 g, 6.0 mmol, yield 38.9 %) (based on 2,3-dimethyloxazolinium iodide). This procedure was also used for syntheses of **196-202**. A single crystal was grown from acetone/hexane for X-ray crystallography. ¹H NMR (300 MHz, CDCl₃): δ 2.77 (t, >NCH₂CH₂-, J = 6.8 Hz, 2H), 2.97 (s, >N-CH₃, 3H), 3.39 (t, >NCH₂CH₂-, J = 6.8 Hz, 2H), 7.07-7.60 (aromatic, 10H), 9.60 (CONHPh, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 170.8 (-CON(CH₃)-), 164.4 (-CONHPh), 136.8, 128.8, 124.6, 119.8 (aromatic), 62.7 (>C(CONHPh)₂), 46.0 (>NCH₂CH₂-), 30.4 (>NCH₃), 28.0 (>NCH₂CH₂-). IR (neat, cm⁻¹): 3366, 3323, 1696, 1676, 1661, 1595, 1546, 1493, 1439, 1402, 1310, 1232, 1180, 755, 690. XRD: CCDC number 794113.

Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-*m*-tolylamide (**196**)

The title compound 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-*m*-tolylamide (**196**) (1.08 g, 73 % yield) was prepared using 2,3-dimethyloxazolinium iodide (**190**) (0.92 g, 4.0 mmol, 1 eq.), Et₃N (0.60 g, 5.9 mmol, 1.5 eq.) and *m*-tolyl isocyanate (1.24 g, 9.13 mmol, 2.25 eq.) by the general procedure. White solid, mp 143-145 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.30 (CH₃O-Ph-, 6H), 2.76 (m, >NCH₂CH₂-, 2H), 2.96 (s, >N-CH₃, 3H), 3.37 (m, >NCH₂CH₂-, 2H), 6.85-7.60 (aromatic), 9.57

(CONHPh, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.8 ($-\text{CON}(\text{CH}_3)-$), 164.3 ($-\text{CONHPh}-m\text{-CH}_3$), 138.5, 136.7, 128.4, 125.3, 120.3, 116.8 (aromatic), 62.7 ($>\text{C}(\text{CONHPh}-m\text{-CH}_3)_2$), 45.9 ($>\text{NCH}_2\text{CH}_2-$), 30.2 ($>\text{NCH}_3$), 27.9 ($>\text{NCH}_2\text{CH}_2-$), 21.1 ($\text{CH}_3\text{-Ph-}$). IR (neat, cm^{-1}): 3314, 1690, 1658, 1609, 1594, 1540, 1485, 1437, 1405, 1305, 1221, 802, 792, 784, 770, 689, 547, 544.

Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(4-fluorophenyl)-amide (**197**)

The title compound 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(4-fluorophenyl)-amide (**197**) (1.01 g, 85.4 % yield) was prepared using 2,3-dimethyloxazolinium iodide (**190**) (0.72 g, 3.2 mmol, 1 eq.), Et_3N (0.48 g, 4.7 mmol, 1.49 eq.) and *p*-fluorophenyl isocyanate (0.98 g, 7.1 mmol, 2.2 eq.) by the general procedure. White solid, mp 132-134 °C. ^1H NMR (300 MHz, CDCl_3): δ 2.68 (t, $>\text{NCH}_2\text{CH}_2-$, 2H, $J = 6.8$ Hz), 2.88 (s, $>\text{N-CH}_3$, 3H), 3.32 (t, $>\text{NCH}_2\text{CH}_2-$, 2H, $J = 6.8$ Hz), 6.80-7.55 (aromatic), 9.49 (CONHPh). ^{13}C NMR (75 MHz, CDCl_3): δ 170.8 ($-\text{CON}(\text{CH}_3)-$), 164.4 ($-\text{CONHPh-}p\text{-F}$), 161.0, 157.7 (carbon connected to F, $J = 244.3$ Hz), 132.93, 132.89 (aromatic carbon, connected to N, $J = 2.8$ Hz), 121.76, 121.65 (aromatic carbon, meta to F, $J = 7.9$ Hz), 115.56, 115.26 (aromatic carbon, ortho to F, $J = 22.5$ Hz), 62.6 ($>\text{C}(\text{CONHPh-}p\text{-F})_2$), 46.1 ($>\text{NCH}_2\text{CH}_2-$), 30.4 ($>\text{NCH}_3$), 28.0 ($>\text{NCH}_2\text{CH}_2-$). IR (neat, cm^{-1}): 3378, 1698, 1612, 1561, 1532, 1502, 1404, 1302, 1221, 1207, 1190, 827, 755, 750, 595, 533.

Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(4-methoxyphenyl)-amide (**198**)

The title compound 1-ethyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(4-methoxyphenyl)-amide (**198**) 0.53 g, yield 62 %) was prepared using 2,3-dimethyloxazolinium iodide (**190**) (0.49 g, 2.2 mmol, 1 eq.), Et₃N (0.32 g, 3.2 mmol, 1.5 eq.) and *p*-methoxyphenyl isocyanate (0.71 g, 4.7 mmol, 2.2 eq.) by the general procedure. White solid, mp 217-218 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.77 (t, >NCH₂CH₂-, 2H), 2.98 (s, >N-CH₃, 3H), 3.41 (>NCH₂CH₂-, 2H), 3.75 (s, -O-CH₃, 6H), 6.84 (d, J = 9.0 Hz, 4H, aromatic), 7.46 (d, J = 9.0 Hz, 4H, aromatic), 9.48 (CONHPh-*p*-OMe). ¹³C NMR (75 MHz, CDCl₃): δ 171.0 (-CON(CH₃)-), 164.4 (-CONHPh-*p*-OMe), 156.4, 130.0, 121.5, 113.8 (aromatic), 62.4 (>C(CONHPh-*p*-OMe)₂), 55.2 (Ph-*p*-OCH₃), 46.1 (>NCH₂CH₂-), 30.4 (>NCH₃), 28.2 (>NCH₂CH₂-). IR (neat, cm⁻¹): 3312, 1699, 1597, 1507, 1406, 1299, 1232, 1171, 1029, 825.

Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-*p*-tolylamide (**199**)

The title compound 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-*p*-tolylamide (**199**) (0.45 g, 67 % yield) was prepared using 2,3-dimethyloxazolinium iodide (**190**) (0.42 g, 1.8 mmol, 1 eq.), Et₃N (0.27 g, 2.7 mmol, 1.4 eq.) and *p*-tolyl isocyanate (0.55 g, 4.0 mmol, 2.2 eq.) by the general procedure. White solid, mp 121-122 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.28 (CH₃-Ph-, 6H), 2.76 (t, >NCH₂CH₂-, J = 6.8 Hz, 2H), 2.98 (s, >N-CH₃, 3H), 3.40 (t, >NCH₂CH₂-, J = 6.8 Hz, 2H), 7.10 (d, J = 8.4 Hz, 4H), 7.43 (d, J = 8.4 Hz, 4H), 9.53 (CONH, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 171.0 (-CON(CH₃)-), 164.5 (-CONHPh-*p*-CH₃), 134.34, 134.30, 129.2, 119.9 (aromatic), 62.6 (>C(CONHPh-*p*-CH₃)₂), 46.1 (>NCH₂CH₂-), 30.4 (>NCH₃), 28.2 (>NCH₂CH₂-), 20.7

(CH₃-Ph-). IR (neat, cm⁻¹): 3317, 1705, 1659, 1599, 1514, 1403, 1317, 1299, 1245, 819, 676.

Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(4-cyanophenyl) amide (**200**) and *N,N'*-bis-(4-cyanophenyl)-2-(3-methyloxazolidin-2-ylidene)-malonamide (**192**)

The title compound 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(4-cyanophenyl)-amide (**200**) (0.25 g, 28 % yield) and *N,N'*-bis-(4-cyanophenyl)-2-(3-methyloxazolidin-2-ylidene)-malonamide (**192**) (0.048 g, 5.4 % yield) were prepared using 2,3-dimethyloxazolinium iodide (**190**) (0.52 g, 2.3 mmol, 1 eq.), Et₃N (0.33 g, 3.2 mmol, 1.4 eq.) and *p*-cyanophenyl isocyanate (0.72 g, 4.8 mmol, 2.1 eq.) by the general procedure. A white cotton like precipitate formed during workup. It was not soluble in either DCM or water. This precipitate was discarded. **200**, white solid, mp 211-212 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 2.75 (t, >NCH₂CH₂-, 2H), 2.86 (s, >N-CH₃, 3H), 3.40 (>NCH₂CH₂-, 2H), 7.78 (d, J = 8.1 Hz, aromatic, 4H), 7.86 (d, J = 8.4 Hz, aromatic, 4H), 10.29 (CONHPh-*p*-CN). ¹³C NMR (75 MHz, DMSO-d₆): δ 168.6 (-CON(CH₃)-), 166.1 (-CONHPh-*p*-CN), 143.1, 133.6, 133.4, 121.1, 120.8, 119.4 (aromatic), 106.2(CN), 66.2 (>C(CONHPh-*p*-CN)₂), 46.5 (>NCH₂CH₂-), 30.6 (>NCH₃), 27.8 (>NCH₂CH₂-). IR (neat, cm⁻¹): 3359, 2224, 1700, 1588, 1509, 1406, 1308, 1243, 1179, 952, 835, 699, 610. **192**, white solid, mp 188-189 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 3.05 (s, >N-CH₃, 3H), 3.97 (t, >NCH₂-, J = 8.9 Hz, 2H), 4.64 (t, -CH₂O-, J = 8.9 Hz, 2H), 7.65-7.80 (aromatic, 8H), 10.34 (CONHPh-*p*-CN, 2H). ¹³C NMR (75 MHz, DMSO-d₆): δ 171.1 (N,O>C=), 165.6 (-CONHPh-*p*-CN), 144.5, 133.1, 119.4, 118.9 (aromatic), 103.0 (CN),

77.4 ($=\text{C}(\text{CONHPh-}p\text{-CN})_2$), 66.6 ($-\text{OCH}_2-$), 51.2 ($\text{N}-\text{CH}_2-$), 37.1 ($>\text{N}-\text{CH}_3$). IR (neat, cm^{-1}): 3394, 2214, 1652, 1558, 1489, 1408, 1311, 1172, 1058, 924, 824, 778.

Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(4-trifluoromethylphenyl)-amide (**201**) and 2-(3-methyloxazolidin-2-ylidene)-*N,N'*-bis-(4-trifluoromethylphenyl)-malonamide (**193**)

The title compound 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(4-trifluoromethylphenyl)-amide (**201**) (0.59 g, 69 % yield) and 2-(3-methyloxazolidin-2-ylidene)-*N,N'*-bis-(4-trifluoromethylphenyl)-malonamide (**193**) (0.12 g, 14 % yield) were prepared using 2,3-dimethyloxazolinium iodide (**190**) (0.41 g, 1.8 mmol, 1 eq.), Et_3N (0.26 g, 2.6 mmol, 1.4 eq.) and 4-trifluoromethylphenyl isocyanate (0.76 g, 4.0 mmol, 2.2 eq.) by the general procedure. **201**, white solid, mp 170-171 °C. ^1H NMR (300 MHz, CDCl_3): δ 2.84 (t, $>\text{NCH}_2\text{CH}_2-$, 2H), 3.05 (s, $>\text{N}-\text{CH}_3$, 3H), 3.49 (t, $>\text{NCH}_2\text{CH}_2-$, 2H), 7.50-7.90 (aromatic, 8H), 9.76 ($\text{CONHPh-}p\text{-CF}_3$). ^{13}C NMR (75 MHz, CDCl_3): δ 170.8 ($-\text{CON}(\text{CH}_3)-$), 164.7 ($-\text{CONHPh-}p\text{-CF}_3$), 139.9 (C para to CF_3), 126.8 (C connecting to CF_3 , split to a quartet, $J = 32.8$ Hz), 126.3 (C ortho to CF_3 , split to a quartet, $J = 3.7$ Hz), 123.9 (CF_3 , split to a quartet, $J = 271.6$ Hz), 119.8 (C meta to CF_3), 63.1 ($=\text{C}(\text{CONHPh-}p\text{-CF}_3)_2$), 46.3 ($>\text{NCH}_2\text{CH}_2-$), 30.7 ($>\text{NCH}_3$), 28.3 ($>\text{NCH}_2\text{CH}_2-$). IR (neat, cm^{-1}): 3346, 3260, 1710, 1666, 1605, 1529, 1407, 1317, 1259, 1158, 1104, 1064, 1016, 836. **193**, white solid, mp 140-141 °C. ^1H NMR (300 MHz, CDCl_3): δ 3.13 (s, $>\text{N}-\text{CH}_3$, 3H), 3.94 (t, $>\text{NCH}_2-$, $J = 8.2$ Hz, 2H), 4.66 (t, $-\text{CH}_2\text{O}-$, $J = 8.2$ Hz, 2H), 7.40-7.80 (aromatic), 10.22 ($\text{CONHPh-}p\text{-CF}_3$, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 168.8 ($\text{N}, \text{O}>\text{C}=\text{O}$), 165.5 ($-\text{CONHPh-}p\text{-CF}_3$), 142.1 (aromatic), 126.0 (aromatic), 124.8 (aromatic), 122.5 (CF_3), 119.8 (aromatic), 66.0 ($=\text{C}(\text{CONHPh-}p\text{-CF}_3)_2$), 51.4 ($-\text{OCH}_2-$), 38.3 ($\text{N}-\text{CH}_2-$), 30.9 ($>\text{N}-$

CH₃). IR (neat, cm⁻¹): 3326, 1652, 1616, 1505, 1436, 1407, 1311, 1252, 1159, 1107, 1057, 935, 837.

Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(4-trifluoromethylphenyl)-amide (**201**) and 2-(3-methyloxazolidin-2-ylidene)-*N,N'*-bis-(4-trifluoromethylphenyl)-malonamide (**193**) by refluxing in THF

The title compound 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(4-trifluoromethylphenyl)-amide (**201**) and 2-(3-methyloxazolidin-2-ylidene)-*N,N'*-bis-(4-trifluoromethylphenyl)-malonamide (**193**) were prepared using 2,3-dimethyloxazolinium iodide (**190**) (0.32 g, 1.4 mmol, 1 eq.), Et₃N (0.21 g, 2.0 mmol, 1.4 eq.) and 4-trifluoromethylphenyl isocyanate (0.60 g, 3.2 mmol, 2.3 eq.) by the general procedure, with refluxing time 13.5 h. Rearranged product **201** (white solid, 0.50 g) was obtained in 75 % yield, and unrearranged product **193** (white solid, 0.034 g) was obtained in 5.1 % yield.

Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(2-bromophenyl)-amide] (**202**) and *N,N'*-bis-(2-bromophenyl)-2-(3-methyloxazolidin-2-ylidene)-malonamide (**194**)

The title compound 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(2-bromophenyl)-amide] (**202**) (0.40 g, 42 % yield) and *N,N'*-bis-(2-bromophenyl)-2-(3-methyloxazolidin-2-ylidene)-malonamide (**194**) (0.28 g, 29 % yield) were prepared using 2,3-dimethyloxazolinium iodide (**190**) (0.44 g, 1.9 mmol, 1 eq.), Et₃N (0.29 g, 2.8 mmol, 1.5 eq.) and 2-bromophenyl isocyanate (0.86 g, 4.2 mmol, 2.2 eq.) by the general procedure. **202**, white solid, mp 166-167 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.90 (t, J = 6.8 Hz, >NCH₂CH₂-, 2H), 3.02 (s, >N-CH₃, 3H), 3.40 (t, J = 6.9 Hz, >NCH₂CH₂-, 2H), 6.98 (td, J = 1.5 Hz (d), J = 7.9 Hz (t), 2H, aromatic), 7.25~7.32 (m, 2H, aromatic),

7.48~7.56 (m, 2H, aromatic), 8.27~8.35 (m, 2H, aromatic), 10.05 (CONHPh-o-Br). ^{13}C NMR (75 MHz, CDCl_3): δ 170.5 ($-\text{CON}(\text{CH}_3)-$), 163.8 ($-\text{CONHPh-o-Br}$), 135.2, 132.4, 128.0, 125.7, 122.0, 114.0 (aromatic), 63.5 ($>\text{C}(\text{CONHPh-o-Br})_2$), 46.3 ($>\text{NCH}_2\text{CH}_2-$), 30.6 ($>\text{NCH}_3$), 26.8 ($>\text{NCH}_2\text{CH}_2-$). IR (neat, cm^{-1}): 3336, 1717, 1662, 1577, 1524, 1432, 1292, 1178, 1022, 944, 756. **194**, white solid, mp 156-157 °C. ^1H NMR (300 MHz, CDCl_3): δ 3.08 (s, $>\text{N-CH}_3$, 3H), 3.87 (t, $>\text{NCH}_2-$, $J = 8.4$ Hz, 2H), 4.60 (t, $-\text{CH}_2\text{O}-$, $J = 8.4$ Hz, 2H), 6.88 (t, $J = 7.1$ Hz, aromatic, 2H), 7.27 (t, $J = 7.3$ Hz, aromatic, 2H), 7.52 (d, $J = 7.5$ Hz, aromatic, 2H), 8.43 (d, $J = 7.9$ Hz, aromatic, 2H), 10.45 (CONHPh-o-Br, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 169.0 ($\text{N,O}>\text{C}=\text{O}$), 165.2 ($-\text{CONHPh-o-Br}$), 137.6, 132.2, 127.8, 123.7, 122.3, 113.6 (aromatic), 79.2 ($=\text{C}(\text{CONHPh-o-Br})_2$), 65.8 ($-\text{OCH}_2-$), 51.2 (N-CH_2-), 38.1 ($>\text{N-CH}_3$). IR (neat, cm^{-1}): 3364, 1643, 1556, 1484, 1424, 1301, 1278, 1060, 1024, 933, 780, 732.

Preparation of 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(2-bromophenyl)-amide] (**202**) using 1,4-dioxane as solvent

The title compound 1-methyl-2-oxo-pyrrolidine-3,3-dicarboxylic acid bis-[(2-bromophenyl)-amide] (**202**) (0.46 g, 68 % yield) was prepared using 2,3-dimethyloxazolinium iodide **190** (0.31 g, 1.4 mmol, 1 eq.), Et_3N (0.20 g, 2.0 mmol, 1.4 eq.) and 2-bromophenyl isocyanate (0.64 g, 3.1 mmol, 2.2 eq.). Anhydrous 1,4-dioxane (21.6 mL) was used as the solvent. The mixture was refluxed under nitrogen for 11.5 h, worked up by general procedure and purified by flash column chromatography over silica gel. Examination of the product's melting point, ^1H NMR, IR proved it to be **202**. **194** was not detected.

Preparation of 2-(3-methyloxazolidin-2-ylidene)-*N,N'*-diphenyl-malonamide (**191**)

The title compound 2-(3-methyloxazolidin-2-ylidene)-*N,N'*-diphenyl-malonamide (**191**) (2.18 g, yield 55 %) was prepared using 2,3-dimethyloxazolinium iodide **190** (2.65 g, 11.7 mmol, 1 eq.), Et₃N (1.59 g, 15.6 mmol, 1.34 eq.), phenyl isocyanate (3.00 g, 24.7 mmol, 2.11 eq.) and 36.4 mL THF. The mixture was stirred at room temperature for 18 h. Workup followed the general procedure for preparation of **195**. Recrystallization from DCM twice gave 2-(3-methyloxazolidin-2-ylidene)-*N,N'*-diphenyl-malonamide (**191**) White solid, mp 158-160 °C. ¹H NMR (300 MHz, CDCl₃): δ 3.06 (s, >N-CH₃, 3H), 3.75 (t, >NCH₂-, J = 8.4 Hz, 2H), 4.48 (t, -CH₂O-, J = 8.4 Hz, 2H), 6.95-7.60 (aromatic), 10.04 (CONHPh, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 168.4 (N,O>C=), 165.6 (-C=CONHPh), 139.0, 128.7, 123.1, 120.4 (aromatic), 79.3 (=C(CONHPh)₂), 65.7 (-OCH₂-), 51.2 (N-CH₂-), 38.0 (>N-CH₃). IR (neat, cm⁻¹): 3320, 3011, 1652, 1584, 1516, 1495, 1436, 1295, 1059, 935, 783, 746. Crystal structure: CCDC number 794114.

Preparation of *N,N'*-diphenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**74**)

2,3,4,4-Tetramethyloxazolinium iodide (**182**) (2.98 g, 11.7 mmol, 1 eq.) was placed in a 100 mL flask, followed by dried THF (30.8 mL), Et₃N (1.58 g, 15.5 mmol, 1.33 eq.) and phenyl isocyanate (3.00 g, 24.7 mmol, 2.11 eq.). The suspension was refluxed for 5 h under nitrogen. Rotary evaporation was used to remove the solvent. Then dichloromethane (19 mL) and saturated NaHCO₃ (30 mL) were added to the residue and the mixture was stirred for 10 min. The organic layer was washed further with brine (2 x 24 mL), and dried over anhydrous Na₂SO₄. After concentrating by rotary evaporation, the crude product was purified by flash column chromatography over silica gel, using mixed

ethyl acetate/hexanes as the eluting solvent. Upon solvent removal, *N,N'*-diphenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**74**) was obtained (3.35 g, yield 78.6 %). This procedure was also used for syntheses of **183-189**. White solid, mp 161-162 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.43 (s, >N-C(CH₃)₂-, 6H), 2.95 (s, >N-CH₃, 3H), 4.25 (s, -OCH₂-, 2H), 7.01-7.63 (aromatic, 10H), 10.02 (CONHPh, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 169.7 (N,O>C=), 167.0 (-CONHPh), 140.6 (aromatic, carbon connecting to N), 130.1 (aromatic, carbon meta to N), 121.9 (aromatic, carbon ortho to N), 124.4 (aromatic, carbon para to N), 82.1 (=C(CONHPh)), 78.5 (-OCH₂-), 63.6 (N-C(CH₃)₂), 32.4 (>N-CH₃), 24.9 (>N-C(CH₃)₂-) IR (neat, cm⁻¹): 3309, 1705, 1589, 1526, 1498, 1439, 1318, 1310, 1262, 1224, 1183, 1176, 751, 734, 693, 686, 564.

Preparation of *N,N'*-di-*m*-tolyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**183**)

The title compound *N,N'*-di-*m*-tolyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**183**) (1.11 g, yield 75.8 %) was prepared using 2,3,4,4-tetramethyloxazolinium iodide (**182**) (0.95 g, 3.7 mmol, 1 eq.), Et₃N (0.55 g, 5.4 mmol, 1.4 eq.) and *m*-tolyl isocyanate (1.14 g, 8.4 mmol, 2.2 eq.) by the general procedure. White solid, mp 160-162 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.31 (s, >N-C(CH₃)₂-, 6H), 2.32 (-Ph-*m*-CH₃, 6H), 2.87 (s, >N-CH₃, 3H), 4.12 (s, -OCH₂-, 2H), 6.80-7.58 (aromatic, 8H), 9.99 (CONHPh-*m*-CH₃, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 167.6 (N,O>C=), 165.4 (-CONHPh-*m*-CH₃), 139.0, 138.2, 128.3, 123.5, 120.8, 117.3 (aromatic), 79.1 (=C(CONHPh-*m*-CH₃)₂), 76.8 (-OCH₂-), 61.9 (N-C(CH₃)₂), 30.7 (>N-CH₃), 23.2 (>N-C(CH₃)₂-), 21.3 (-PhOCH₃) IR (neat, cm⁻¹): 3310, 1653, 1588, 1527, 1485, 1424, 1303, 1256, 1243, 1156, 1058, 782, 744, 692, 566, 557.

Preparation of *N,N'*-bis-(4-fluorophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**184**)

The title compound *N,N'*-bis-(4-fluorophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**184**) (0.66 g, yield 76 %) was prepared using 2,3,4,4-tetramethyloxazolinium iodide (**182**) (0.55 g, 2.2 mmol, 1 eq.), Et₃N (0.30 g, 2.9 mmol, 1.4 eq.) and *p*-fluorophenyl isocyanate (0.69 g, 5.0 mmol, 2.3 eq.) by the general procedure. White solid, mp 135-137 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.27 (s, >N-C(CH₃)₂-, 6H), 2.81 (s, >N-CH₃, 3H), 4.10 (s, -OCH₂-, 2H), 6.80 -7.58 (aromatic, 8H), 9.91 (CONHPh-*p*-F, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 167.8 (N,O>C=), 165.5 (-C=CONHPh-*p*-F), 160.1, 156.9 (carbon connected to F, J = 241.4 Hz), 135.06, 135.02 (aromatic carbon, connected to N, J = 2.7 Hz), 122.08, 121.98 (aromatic carbon, meta to F, J = 7.7 Hz), 115.15, 114.86 (aromatic carbon, ortho to F, J = 22.2 Hz), 78.6 (=C(CONHPh-*p*-F)₂), 76.9 (-OCH₂-), 62.1 (N-C(CH₃)₂), 30.8 (>N-CH₃), 23.2 (>N-C(CH₃)₂-). IR (neat, cm⁻¹): 3246, 1642, 1545, 1532, 1498, 1472, 1429, 1409, 1400, 1309, 1301, 1208, 1187, 1054, 836, 811, 783, 689.

Preparation of *N,N'*-bis-(4-methoxyphenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**185**)

The title compound *N,N'*-bis-(4-methoxyphenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**185**) (0.34 g, yield 64 %) was prepared using 2,3,4,4-tetramethyloxazolinium iodide (**182**) (0.32 g, 1.3 mmol, 1 eq.), Et₃N (0.18 g, 1.8 mmol, 1.4 eq.) and *p*-methoxyphenyl isocyanate (0.42 g, 2.8 mmol, 2.2 eq.) by the general procedure. White solid, mp 226-227 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.37 (s, >N-C(CH₃)₂-, 6H), 2.92 (s, >N-CH₃, 3H), 3.78 (s, -O-CH₃, 6H), 4.19 (s, -OCH₂-, 2H), 6.86

(d, $J = 8.3$ Hz, 4H), 7.48 (d, $J = 8.3$ Hz, 4H), 9.92 (CONHPh-*p*-OMe, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 167.8 (N,O> $\text{C}=\text{O}$), 165.7 ($-\text{CONHPh-}p\text{-OMe}$), 155.6 (aromatic, carbon para to N), 132.4 (aromatic, carbon connecting to N), 122.4 (aromatic, carbon ortho to N), 113.9 (aromatic, meta to N), 79.0 ($=\text{C}(\text{CONHPh-}p\text{-OMe})_2$), 77.6 ($-\text{OCH}_2-$), 62.0 (N- $\text{C}(\text{CH}_3)_2$), 55.4 (Ph-*p*-O CH_3), 30.9 ($>\text{N-CH}_3$), 23.5 ($>\text{N-C}(\text{CH}_3)_2-$). IR (neat, cm^{-1}): 3288, 1641, 1537, 1509, 1409, 1243, 1173, 1109, 1029, 985, 822, 782, 726.

Preparation of *N,N'*-Di-*p*-tolyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (186)

The title compound *N,N'*-di-*p*-tolyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**186**) (0.32 g, yield 69.2 %) was prepared using 2,3,4,4-tetramethyloxazolinium iodide (**182**) (0.30 g, 1.2 mmol, 1 eq.), Et_3N (0.18 g, 1.8 mmol, 1.5 eq.) and *m*-tolyl isocyanate (0.38 g, 2.8 mmol, 2.4 eq.) by the general procedure. White solid, mp 157-158 °C. ^1H NMR (300 MHz, CDCl_3): δ 1.31 (s, $>\text{N-C}(\text{CH}_3)_2-$, 6H), 2.28 ($-\text{PhCH}_3$, 6H), 2.86 (s, $>\text{N-CH}_3$, 3H), 4.12 (s, $-\text{OCH}_2-$, 2H), 7.08 (d, $J = 8.3$ Hz, 4H), 7.43 (d, $J = 8.3$ Hz, 4H), 9.96 (CONHPh-*p*-CH $_3$, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 167.6 (N,O> $\text{C}=\text{O}$), 165.4 ($-\text{CONHPh-}p\text{-CH}_3$), 136.4, 132.1, 129.0, 120.3 (aromatic), 79.0 ($=\text{C}(\text{CONHPh-}p\text{-CH}_3)_2$), 76.7 ($-\text{OCH}_2-$), 61.8 (N- $\text{C}(\text{CH}_3)_2$), 30.7 ($>\text{N-CH}_3$), 23.2 ($>\text{N-C}(\text{CH}_3)_2-$), 20.6 ($-\text{PhCH}_3$). IR (neat, cm^{-1}): 3306, 1652, 1583, 1506, 1433, 1402, 1310, 1238, 1184, 1056, 806, 782.

Preparation of *N,N'*-bis-(4-cyanophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (187)

The title compound *N,N'*-bis-(4-cyanophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**187**) (0.17 g, yield 36 %) was prepared using 2,3,4,4-

tetramethyloxazolinium iodide (**182**) (0.29 g, 1.1 mmol, 1 eq.), Et₃N (0.17 g, 1.7 mmol, 1.5 eq.) and *p*-cyanophenyl isocyanate (0.38 g, 2.6 mmol, 2.2 eq.) by the general procedure. White cotton like precipitate formed during workup. It was not soluble in both DCM and water. This precipitate was discarded. White solid, mp 193-194 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 1.37 (s, >N-C(CH₃)₂-, 6H), 2.92 (s, >N-CH₃, 3H), 4.38 (s, -OCH₂-, 2H), 7.68 (d, 4H, J = 7.9 Hz), 7.76 (d, 4H, J = 7.5 Hz), 10.28 (CONHPh-*p*-CN, 2H). ¹³C NMR (75 MHz, DMSO-d₆): δ 169.9 (N,O>C=), 165.6 (-CONHPh-*p*-CN), 144.5, 133.0, 119.4, 118.8 (aromatic), 103.0 (CN), 78.1 (=C(CONHPh-*p*-CN)₂), 77.1 (-OCH₂-), 62.9 (N-C(CH₃)₂-), 30.6 (>N-CH₃), 22.8, 23.0 (>N-C(CH₃)₂-). IR (neat, cm⁻¹): 3390, 2214, 1659, 1495, 1427, 1409, 1314, 1236, 1173, 1054, 958, 839, 803, 777.

Preparation of *N,N'*-bis-(4-trifluoromethylphenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**188**)

The title compound *N,N'*-bis-(4-trifluoromethylphenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**188**) (0.34 g, yield 82 %) was prepared using 2,3,4,4-tetramethyloxazolinium iodide (**182**) (0.21 g, 0.82 mmol, 1 eq.), Et₃N (0.12 g, 1.2 mmol, 1.4 eq.) and *p*-trifluoromethylphenyl isocyanate (0.36 g, 1.9 mmol, 2.3 eq.) by the general procedure. White solid, mp 174-175 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.46 (s, >N-C(CH₃)₂-, 6H), 2.97 (s, >N-CH₃, 3H), 4.32 (s, -OCH₂-, 2H), 7.50-7.72 (aromatic, 8H), 10.20 (CONHPh-*p*-CF₃, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 168.3 (N,O>C=), 165.6 (-CONHPh-*p*-CF₃), 142.2 (aromatic, C para to CF₃), 126.0 (aromatic, C ortho to CF₃, quartet, J = 3.8 Hz), 124.5 (aromatic, C connecting to CF₃, quartet, J = 32.6 Hz), 122.5 (CF₃), 119.8 (aromatic, C meta to CF₃), 79.1 (=C(CONHPh-*p*-CF₃)₂), 77.3 (-

OCH₂-), 62.6 (N-C(CH₃)₂), 31.2 (>N-CH₃), 23.6 (>N-C(CH₃)₂-). IR (neat, cm⁻¹): 3213, 3114, 3047, 1632, 1598, 1533, 1408, 1313, 1257, 1104, 1058, 1014, 839.

Preparation of *N,N'*-bis-(2-bromophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**189**)

The title compound *N,N'*-bis-(2-bromophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (**189**) (0.39 g, yield 76 %) was prepared using 2,3,4,4-tetramethyloxazolinium iodide (**182**) (0.25 g, 0.98 mmol, 1 eq.), Et₃N (0.14 g, 1.4 mmol, 1.4 eq.) and *p*-trifluoromethylphenyl isocyanate (0.45 g, 2.2 mmol, 2.2 eq.) by the general procedure. White solid, mp 145-146 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.39 (s, >N-C(CH₃)₂-, 6H), 2.92 (s, >N-CH₃, 3H), 4.27 (s, -OCH₂-, 2H), 6.86 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.8 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 8.44 (d, J = 8.3 Hz, 2H), 10.43 (s, CONHPh-o-Br, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 168.6 (N,O>C=), 165.2 (-CONHPh-o-Br), 137.6, 132.0, 127.7, 123.4, 122.1, 113.4 (aromatic), 79.0 (=C(CONHPh-o-Br)₂), 77.0 (-OCH₂-), 62.4 (N-C(CH₃)₂), 31.0 (>N-CH₃), 23.3 (>N-C(CH₃)₂-). IR (neat, cm⁻¹): 3359, 2969, 1627, 1568, 1505, 1431, 1301, 1056, 1021, 836, 782, 764, 742.

Bu₄NI catalyzed rearrangement of 2-(3-methyloxazolidin-2-ylidene)-*N,N'*-diphenyl-malonamide (**191**)

2-(3-Methyloxazolidin-2-ylidene)-*N,N'*-diphenyl-malonamide (**191**) (0.16 g, 0.49 mmol, 1 eq.) and Bu₄NI (0.015 g, 0.040 mmol, 0.08 eq.) were refluxed in 7.4 mL THF for 17 h. Workup followed the general procedure for preparation of **195**. Chromatography (1:1 volume ratio acetone/hexanes as the eluting solvent) and solvent removal gave **195** (0.098 g white solid) in 59 % yield, and 0.044 g (27 %) starting material **191** was recovered.

Preparation of *N*-(2-bromophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetamide (210)

2,3,4,4-Tetramethyloxazolinium iodide (**182**) (3.36 g, 13.0 mmol, 1 eq.) was put into a flask, followed by 90 mL dried THF. NaH (1.13 g, 28.2 mmol, 2.17 eq.) was added in one portion to the mixture. Hydrogen bubbles were generated. The mixture was stirred for 4 h under nitrogen protection. The solid settled to the bottom and the top liquid became clear. The top layer (25 mL) was removed to another flask via a syringe. 2-Bromophenyl isocyanate (0.840 g, 4.11 mmol, 1.14 eq.), diluted in 26 mL THF, was added dropwise to the flask, over a period of 3 h with stirring, at room temperature. The mixture was stirred for 12 h. Rotary evaporation was used to remove the solvent. Then DCM (19 mL) and water (25 mL) were added and the mixture stirred for 10 min. The organic layer was washed further with water (25 mL), and dried over anhydrous Na₂SO₄. After concentration by rotary evaporation, the crude product was purified by flash column chromatography over SiO₂ gel, using 1:2 volume ratio acetone/hexanes as the eluting solvent. *N*-(2-Bromophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetamide (**210**) was obtained, yield 32 % (based on the amount of cyclic ketene-*N,O*-acetal **27** in the 25 mL cyclic ketene-*N,O*-acetal/THF mixture, assuming 100 % yield of the cyclic ketene-*N,O*-acetal generation step). ¹H NMR (300 MHz, CDCl₃): δ 8.88 (s, NH), 8.53 (d, 1H), 7.45 (d, 1H), 7.21 (t, 1H), 6.80 (t, 1H), 4.12 (s, -CH₂-, 2H), 4.00 (s, =CHCONH-, 1H), 2.56 (s, >N-CH₃, 3H), 1.17 (>N-C(CH₃)₂-). ¹³C NMR (300 MHz, CDCl₃): δ 165.4 (-CONHPh or N,O>C=), 161.5 (-CONHPh or N,O>C=), 137.5, 131.4, 127.4, 122.3, 120.6, 111.7 (aromatic), 78.1 (=CCONHPh), 69.3 (s, -CH₂-, 2H), 59.7 (>N-C(CH₃)₂-), 25.9 (>N-CH₃), 21.9 (>N-C(CH₃)₂-). IR (neat, cm⁻¹): 2971, 1689, 1558, 1495, 1432,

1137, 1015, 990, 865, 813, 749, 577. mp 176-177 °C. 1,3-Bis-(2-bromophenyl)-1-[2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetyl]-urea (**212**) was also obtained in 2 % yield.

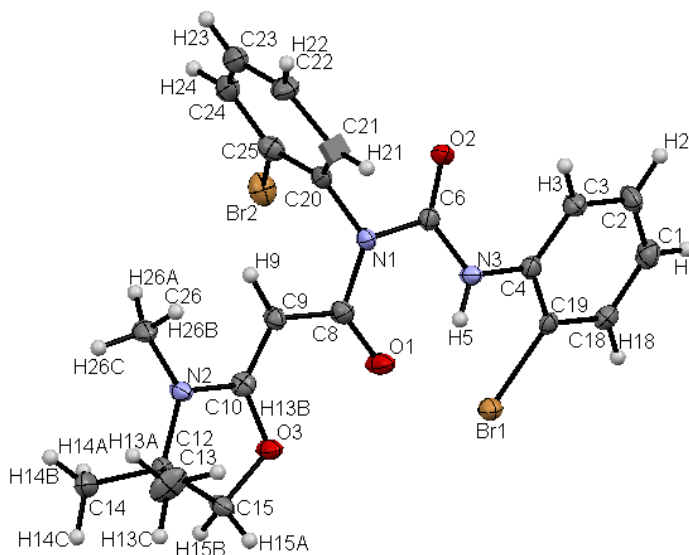


Figure 2.6 The crystal structure of 1,3-bis-(2-bromophenyl)-1-[2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetyl]-urea (**212**)

Attempted intramolecular Heck reaction of *N*-(2-bromophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetamide (**210**)

N-(2-Bromophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetamide (**210**) (0.275 g, 0.85 mmol, 1 eq.) was put into a flask, followed by palladium acetate (0.026 g, 0.11 mmol, 0.13 eq.), triphenyl phosphine (0.128 g, 0.48 mmol, 0.57 eq.) and dried CH₃CN (17 mL). A white greenish suspension was obtained upon stirring. The mixture was degassed by dried nitrogen for 10 minutes, followed by addition of triethylamine (0.202 g, 2.00 mmol, 2.35 eq.) in one portion. The mixture was refluxed for 11.5 h under nitrogen protection. Rotary evaporation was used to remove the solvent. DCM (11 mL) and deionized water (20 mL) were added and stirred for 10 min. The organic layer was washed further with 20 mL deionized water, and dried over Na₂SO₄. After condensation

with rotary evaporation, the crude product was purified by flash column chromatography over SiO₂ gel, using acetone/hexanes (1:2.5 volume ratio) as eluting solvent. *N*-(2-bromophenyl)-acetamide (**213**) (25 mg, white solid, mp 98-100 °C) was obtained in yield 13.8 %. ¹H NMR (300 MHz, CDCl₃): δ 8.33 (d, J = 8.1 Hz, 1H), 7.63 (s, NH, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.32 (t, J = 7.4 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 2.25 (s, CH₃CO, 3H). Another component, 0.103 g, was unidentifiable.

Preparation of 1-phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-ethanone (**90**) from *in situ* generated 3,4,4-trimethyl-2-methylene-oxazolidine (**27**)

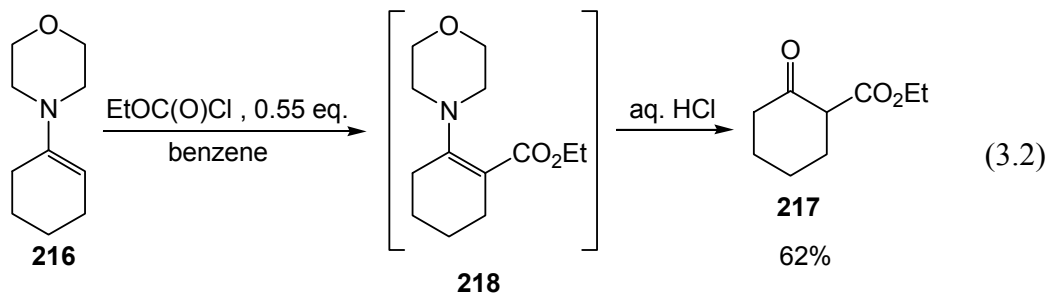
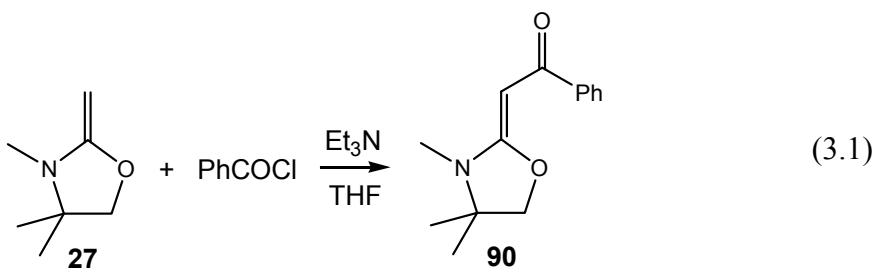
2,3,4,4-Tetramethyloxazolinium iodide (12.7 g, 49.8 mmol, 1 eq.) was placed into a 250 mL flask, followed by dried THF (199 mL), triethylamine (11.3 g, 111 mmol, 2.23 eq.). Benzoyl chloride (7.50 g, 52.8 mmol, 1.06 eq.) was added dropwise to the mixture over 22 min, under nitrogen. The suspension was refluxed for 5 h under nitrogen. Rotary evaporation removed the solvent. Dichloromethane (38 mL) and deionized water (50 mL) were added to the residue and the mixture was stirred for 10 min. The organic layer was washed further with water (50 mL), and dried over anhydrous Na₂SO₄. After concentrating by rotary evaporation, the crude product was purified by flash column chromatography over silica gel, using mixed ethyl acetate/hexanes as the eluting solvent to obtain 1-phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-ethanone (**90**) (white solid, 4.06 g, 17.6 mmol), yield 35.3 %. Melting point and ¹H NMR matched the reported data for this compound.^{14e}

CHAPTER III

REACTIONS OF CYCLIC KETENE-*N,O*-ACETALS WITH CHLOROFORMATES

Introduction

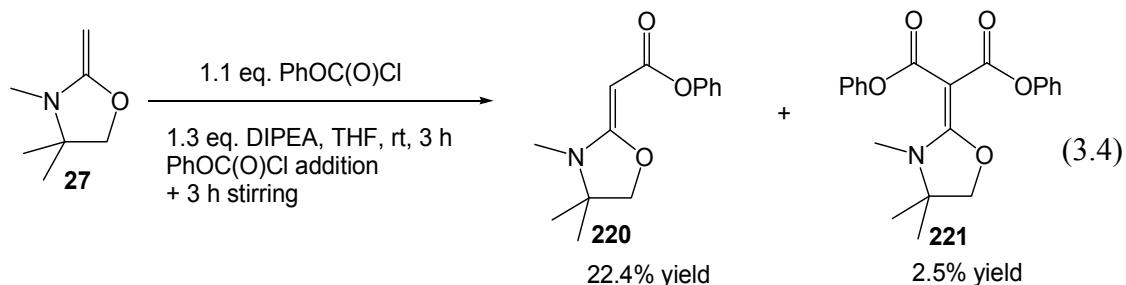
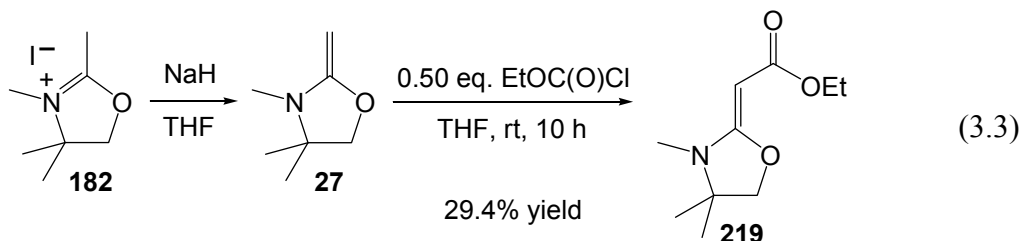
The monobenzoylation of cyclic ketene-*N,O*-acetal **27** has previously been achieved in Pittman's lab^{14e,19} (Equation 3.1). This reaction displays the nucleophilicity of cyclic ketene-*N,O*-acetals towards benzoyl chloride. Can chloroformates, weaker electrophiles than benzoyl chloride, react in a similar manner with cyclic ketene-*N,O*-acetal **27**? This has not been demonstrated but it appears likely because the morpholine enamine of cyclohexanone **216** reacted with 0.5 equivalent of ethyl chloroformate to form 2-carbethoxycyclohexanone (**217**) via a β -alkoxycarbonylated intermediate **218**⁴⁹ (Equation 3.2).

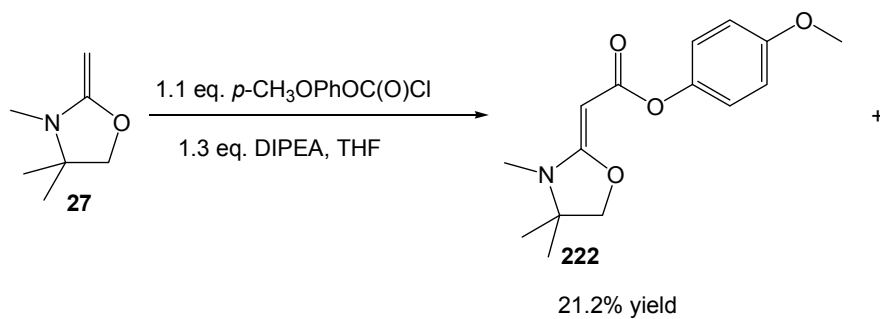


Since cyclic ketene-*N,O*-acetals are stronger nucleophiles than enamines due to the effects of two electron donating heteroatoms (N and O), cyclic ketene-*N,O*-acetals should react with chloroformates. Therefore, this chemistry was explored.

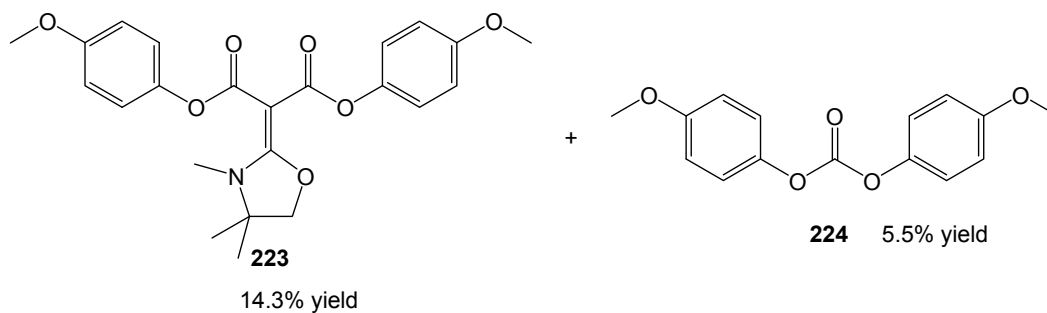
Results and discussion

Two cyclic ketene-*N,O*-acetals, **56** and **27**, and four chloroformates (ethyl chloroformate, phenyl chloroformate, *p*-methoxyphenyl chloroformate and *p*-nitrophenyl chloroformate) were employed to investigate cyclic ketene-*N,O*-acetal/chloroformate chemistry. Eight reactions were performed. The results are shown in Equations 3.3 - 3.10.

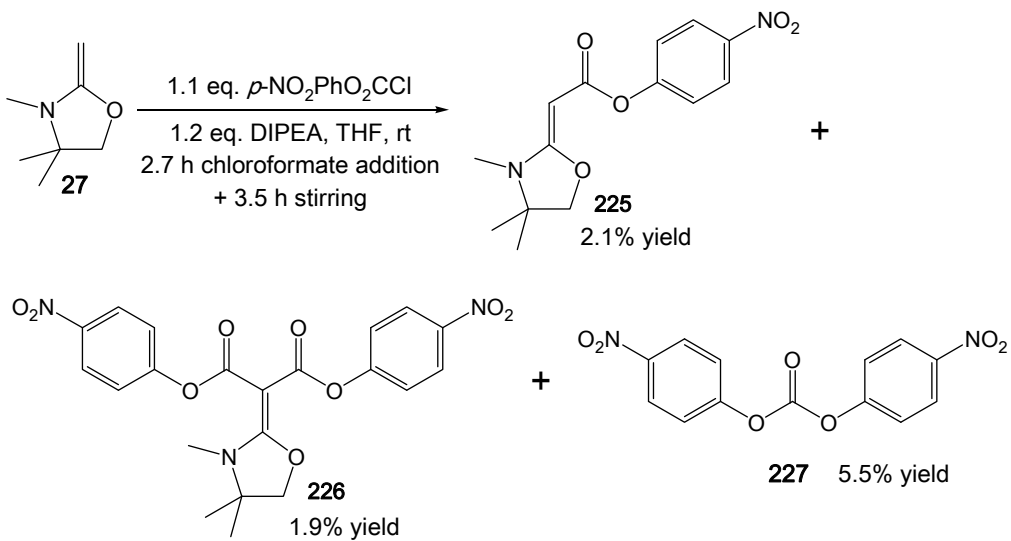




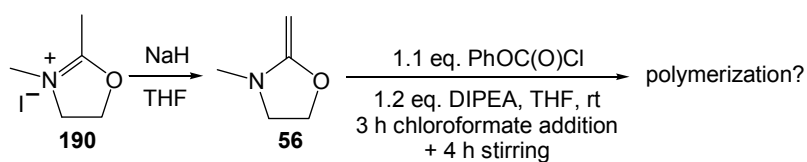
(3.5)



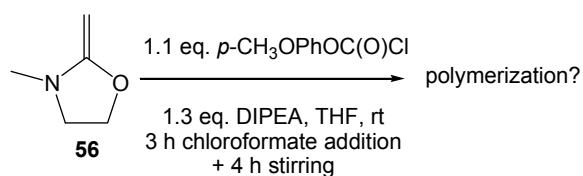
(3.6)

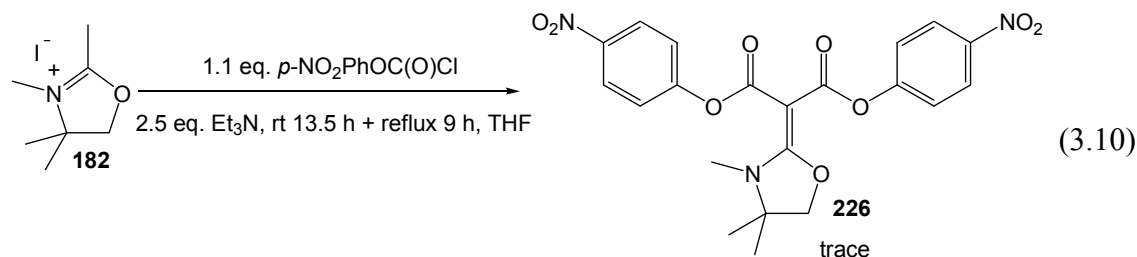
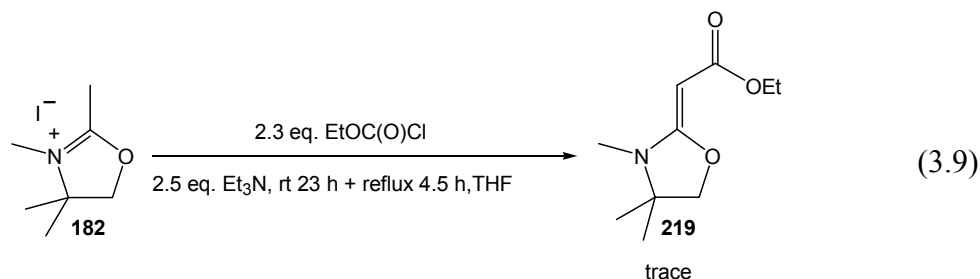


(3.7)



(3.8)





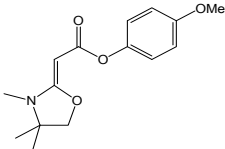
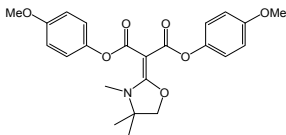
In Equations 3.3 to 3.6, cyclic ketene-*N,O*-acetal **27** was generated in advance by the reaction of 2,3,4,4-tetramethyloxazolinium iodide (**182**) with sodium hydride. However, **27** was not first purified by distillation. Instead, the **27**/THF solution was simply taken by a syringe for use in subsequent reactions. In the reaction of **27** with ethyl chloroformate (Equation 3.3), no base was used. Instead, 2 equivalents of cyclic ketene-*N,O*-acetal **27** was reacted with 1 equivalent of ethyl chloroformate. This was to see if **27** itself can act as the base to remove the β -H after initial β -carbon acylation occurs. This reaction went as expected to form **219**. Reactions of **27** with phenyl chloroformate (Equation 3.4), *p*-methoxyphenyl chloroformate (Equation 3.5) and *p*-nitrophenyl chloroformate (Equation 3.6), in the presence of *N,N*-diisopropylethylamine (DIPEA) as the base, all gave both β -mono aryloxycarbonylated and β -diaryloxycarbonylated adducts (phenyl chloroformate, mono-substituted adduct **220** 22.4 %, di-substituted adduct **221** 2.5 %; *p*-methoxyphenyl chloroformate, mono-substituted adduct **222** 21.2 %, di-substituted adduct **223** 14.3 %; *p*-nitrophenyl chloroformate, mono-substituted adduct **225** 2.1 %, di-substituted adduct **226** 1.9 %). Small amounts of di-(4-methoxyphenyl)

carbonate (**224**) and di-(4-nitrophenyl) carbonate (**227**) were also isolated (Equation 3.5 and 3.6).

At first, it seems counterintuitive that cyclic ketene-*N,O*-acetal **27** would undergo β,β -bisaryloxyacylation with chloroformates. β,β -Diacylated or β,β -dibenzoylated adducts were not observed in reactions of cyclic ketene-*N,O*-acetals with aliphatic acid chlorides or benzoyl chlorides,^{14e,19} which are stronger electrophiles, under similar reaction conditions. However, observation of β,β -bisaryloxyacylation is in accord with a higher nucleophilicity of β -ester-substituted cyclic ketene-*N,O*-acetals versus their mono β -keto substituted cyclic ketene-*N,O*-acetal counterparts. The stronger electron withdrawing keto function reduced the nucleophilicity of the β -carbon of the mono-acylated cyclic ketene-*N,O*-acetals obtained from acid chlorides. This is also reflected in the β -hydrogen chemical shift for β -ester-substituted versus β -keto-substituted cyclic ketene-*N,O*-acetals. The chemical shift of the β -hydrogen of a β -ester-substituted cyclic ketene-*N,O*-acetal is about 4 ppm, whereas that of a β -keto-substituted cyclic ketene-*N,O*-acetal is about 5 ppm.

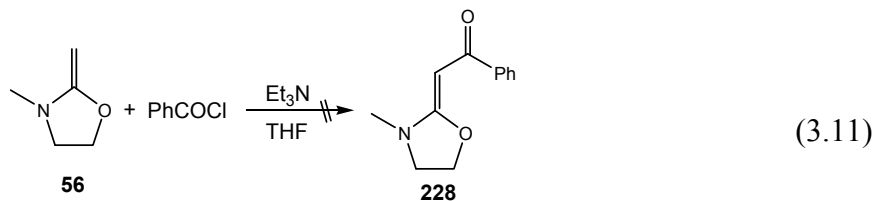
Examination of the crystal structures (Table 3.1) for **222** and **223** revealed that the bis-adduct **223** has a longer exocyclic carbon-carbon double bond, and the plane defined by the two carbonyl carbons and the β -carbon exhibits a large out-of-plane twist angle with respect to the five-membered ring. This means β,β -bis-adduct **223** has a more polarized carbon-carbon double bond with a lower bond order, and is thus more easily twisted.

Table 3.1 Comparison of carbon-carbon double bond lengths and twist angles^a for **222** and **223**

β -substituted cyclic ketene- <i>N,O</i> -acetal	Exocyclic C=C bond length (Å)	Twist angle (°)
 <p>222</p>	1.369	3.34
 <p>223</p>	1.409	32.18

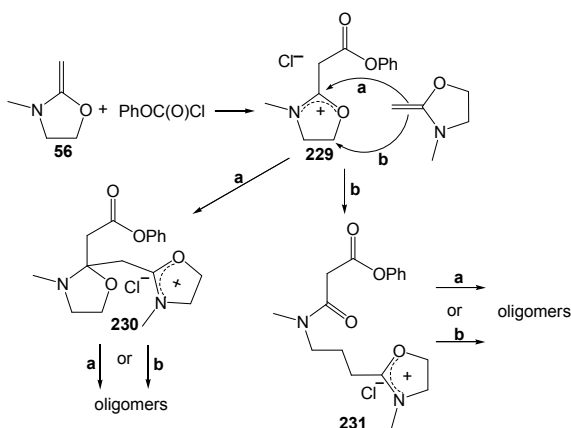
^aA twist angle is defined as the angle between the bisectors of the 1,1- and the 2,2-substituent on a Newman diagram projecting down the C=C bond of the alkene.

Cyclic ketene-*N,O*-acetal **56**, which has two hydrogens instead of two methyl groups at C-4, demonstrated totally different behavior than **27** in reactions with chloroformates (Equations 3.7-3.8). Pasty substances were invariably formed. These are likely to be low molecular weight polymers. The same phenomenon has been observed during attempted benzoylation of cyclic ketene-*N,O*-acetal **56**^{14e} (Equation 3.11).



A suggested oligomerization/polymerization route for cyclic ketene-*N,O*-acetal **56** is shown in Scheme 3.1. Upon formation of cation **237** via nucleophilic attack of **56** on the electrophile, phenyl chloroformate, another molecule of **56** may attack via route **a** or

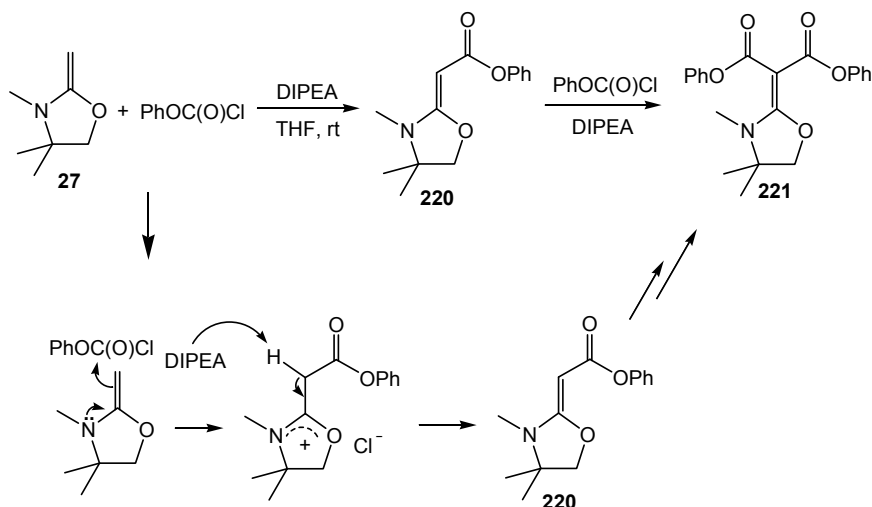
b, forming **230** or **231**. This process may continue to form oligomers. This route may dominate over the rapid deprotonation of a β -hydrogen from **229** by the added base, DIPEA, which would lead to β -substitution. Chain growth would continue until either deprotonation or reaction with an anion stopped the chain. The absence of the two methyl groups at C-4 plays a pivotal role in determining the reaction paths. When two C-4 methyl groups are present (as in cyclic ketene-*N,O*-acetal **27**), the polymerization paths **a** and **b** are hindered. Thus, deprotonation of β -hydrogen by DIPEA dominates (some competing polymerization might still occur) to give β -aryloxycarbonylation products.



Scheme 3.1 A suggested mechanism for polymerization of cyclic ketene-*N,O*-acetal **56**

The reaction of ethyl chloroformate with **27**, generated *in situ* from 2,3,4,4-tetramethyloxazolinium iodide and triethylamine in refluxing THF, gave only a trace of the β -mono ester **219** (Equation 3.9). The reaction of *p*-nitrophenyl chloroformate with *in situ* generated **27** gave a trace of **226** along with unidentifiable products (Equation 3.10).

A mechanism for the reaction of cyclic ketene-*N,O*-acetal **27** with chloroformates (using phenyl chloroformate as an example) is proposed in Scheme 3.2.



Scheme 3.2 Proposed mechanism for reaction of cyclic ketene-*N,O*-acetal **27** with phenyl chloroformate

In conclusion, cyclic ketene-*N,O*-acetal **27**, which has two methyl groups at C-4, reacts with ethyl chloroformate to form a β -mono ethoxycarbonylation adduct **219**. It also reacts with aryl chloroformates to form both mono and di-aryloxycarbonylation adducts. The two methyl groups at C-4 of **27** hinder oligomerization which otherwise would compete. These adducts are push-pull molecules and this chemistry might have application in organic nonlinear optical materials.⁴ In contrast, cyclic ketene-*N,O*-acetal **56**, which does not have two methyl groups at C-4, undergoes cationic polymerization under identical conditions. This highlighted the importance of substituent effects on the cyclic ketene-*N,O*-acetal reaction paths.

Experimental

Preparation of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid ethyl ester (**219**)

2,3,4,4-Tetramethyloxazolinium iodide (**182**) (3.21 g, 12.6 mmol, 1 eq.) was put into a flask, followed by 61 mL dried THF. NaH (0.81 g, 1.6 eq.) was added in one portion to the mixture. Hydrogen bubbles were generated. The mixture was stirred for 4.5 h under nitrogen protection. The solid settled to the bottom and the top liquid became clear. The top layer liquid (55 mL) was removed to another flask via a syringe. Ethyl chloroformate (0.63 g, 0.50 eq.), diluted in 8.5 mL THF, was added dropwise to the flask over a period of 17 min with stirring at room temperature. The mixture was stirred 10 h. Rotary evaporation was used to remove the solvent. DCM (23 mL) and water (30 mL) were added and the mixture stirred for 10 min. The organic layer was washed further with brine (2 x 24 mL), and dried over anhydrous Na₂SO₄. After concentration by rotary evaporation, the crude product was purified by flash column chromatography over SiO₂ gel, using ethyl acetate as the eluting solvent. (3,4,4-Trimethyloxazolidin-2-ylidene)-acetic acid ethyl ester (**219**) (0.33 g, light yellow liquid) was obtained, yield 29.4 % (based on ethyl chloroformate) or 14.7 % (based on **27**). ¹H NMR (300 MHz, CDCl₃): δ 4.18 (s, -O-CH₂-, 2H), 4.10 (q, *J* = 7.10 Hz, -O-CH₂-CH₃, 2H), 3.96 (s, =CH-C(=O)-, 1H), 2.64 (s, >N-CH₃, 3H), 1.26 (>N-C(CH₃)₂-, 6H), 1.24 (t, *J* = 7.12 Hz, -CH₂-CH₃, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 167.4 (-C(=O)OEt or N,O>C=), 165.5 (-C(=O)OEt or N,O>C=), 78.4 (=CH-CO-), 63.3 (>N-C(CH₃)₂-), 59.8 (-C(=O)O-CH₂- or -O-CH₂-), 58.0 (-C(=O)O-CH₂- or -O-CH₂-), 26.2 (>N-CH₃), 22.5 (>N-C(CH₃)₂-), 14.4 (-COO-CH₂-

$\underline{\text{CH}_3}$). IR (neat, cm^{-1}): 2972, 1690, 1592, 1439, 1261, 1136, 1094, 1050, 1023, 988, 770, 704.

Preparation of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid phenyl ester (**220**) and 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid diphenyl ester (**221**)

2,3,4,4-Tetramethyloxazolinium iodide (**182**) (3.04 g, 11.9 mmol, 1 eq.) was put into a flask, followed by dried THF 150 mL. NaH (0.79 g, 1.7 eq.) was added in one portion to the mixture. Hydrogen bubbles were generated. The mixture was stirred for 14 h under nitrogen. After the solid in the mixture settled, the top layer liquid (95 mL) was removed by a syringe and then added dropwise to phenyl chloroformate (1.35 g, 1.12 eq.)/DIPEA (1.26 g, 1.29 eq.)/33 mL THF, over a period of 3 h, with stirring, at ice bath temperature. The mixture was stirred further for 3 h at room temperature. Workup followed the general procedure as stated for preparation of **219**. Acetone/hexanes (1:1.75 volume ratio) mixed solvent was used as the eluting solvent for column chromatography. (3,4,4-Trimethyloxazolidin-2-ylidene)-acetic acid phenyl ester (**220**) (0.42 g, white solid, mp 111-112 °C) was the first component to be eluted, yield 22 %. ^1H NMR (300 MHz, CDCl_3 , Figure 3.1): δ 4.17 (s, $-\underline{\text{CH}_2}-$, 2H), 4.15 (s, $=\underline{\text{CHCOOPh}}$, 1H), 2.65 (s, $>\text{N}-\text{CH}_3$, 3H), 1.22 ($>\text{N}-\text{C}(\text{CH}_3)_2-$, 6H), 7.08-7.40 (aromatic, 5H). ^{13}C NMR (75 MHz, CDCl_3 , Figure 3.2): δ 166.4 ($-\underline{\text{COOPh}}$ or $\text{N},\text{O}>\underline{\text{C}}=$), 165.4 ($-\underline{\text{COOPh}}$ or $\text{N},\text{O}>\underline{\text{C}}=$), 151.5, 128.6, 124.0, 121.8 (aromatic), 78.6 ($=\underline{\text{CCOOPh}}$), 62.4 ($-\text{CH}_2\text{O}-$ or $>\text{N}-\underline{\text{C}}(\text{CH}_3)_2-$), 60.1 ($-\text{CH}_2\text{O}-$ or $>\text{N}-\underline{\text{C}}(\text{CH}_3)_2-$), 26.2 ($>\text{N}-\text{CH}_3$), 22.6 ($>\text{N}-\text{C}(\underline{\text{CH}_3})_2-$). IR (neat, cm^{-1}): 2976, 1702, 1602, 1576, 1492, 1205, 1124, 1104, 1020, 984, 956, 931, 912, 887, 864, 796, 757, 703, 687, 672. 2-(3,4,4-Trimethyloxazolidin-2-ylidene)-malonic acid diphenyl ester (**221**) (0.069 g, white solid, mp 158-159 °C) was the second component to be eluted, yield 2.5

% ^1H NMR (300 MHz, CDCl_3 , Figure 3.3): δ 7.11~7.39 (aromatic, 10H), 4.19 (s, $-\text{CH}_2-$, 2H), 2.92 (s, $>\text{N}-\text{CH}_3$, 3H), 1.30 ($>\text{N}-\text{C}(\text{CH}_3)_2-$, 6H). ^{13}C NMR (75 MHz, CDCl_3 , Figure 3.4): δ 171.6 ($-\text{COOPh}$), 164.8 ($\text{N}, \text{O}=\text{C}=\text{}$), 151.5 (aromatic, carbon connected to O), 128.9 (aromatic), 124.6 (aromatic), 121.8 (aromatic), 77.4 ($=\text{C}(\text{COOPh})_2$), 72.8 (s, $-\text{CH}_2-$, 2H), 62.8 ($>\text{N}-\text{C}(\text{CH}_3)_2$), 30.0 ($>\text{N}-\text{CH}_3$), 23.1 ($>\text{N}-\text{C}(\text{CH}_3)_2$). IR (neat, cm^{-1}): 1677, 1576, 1434, 1282, 1183, 1012, 836, 751, 732, 689.

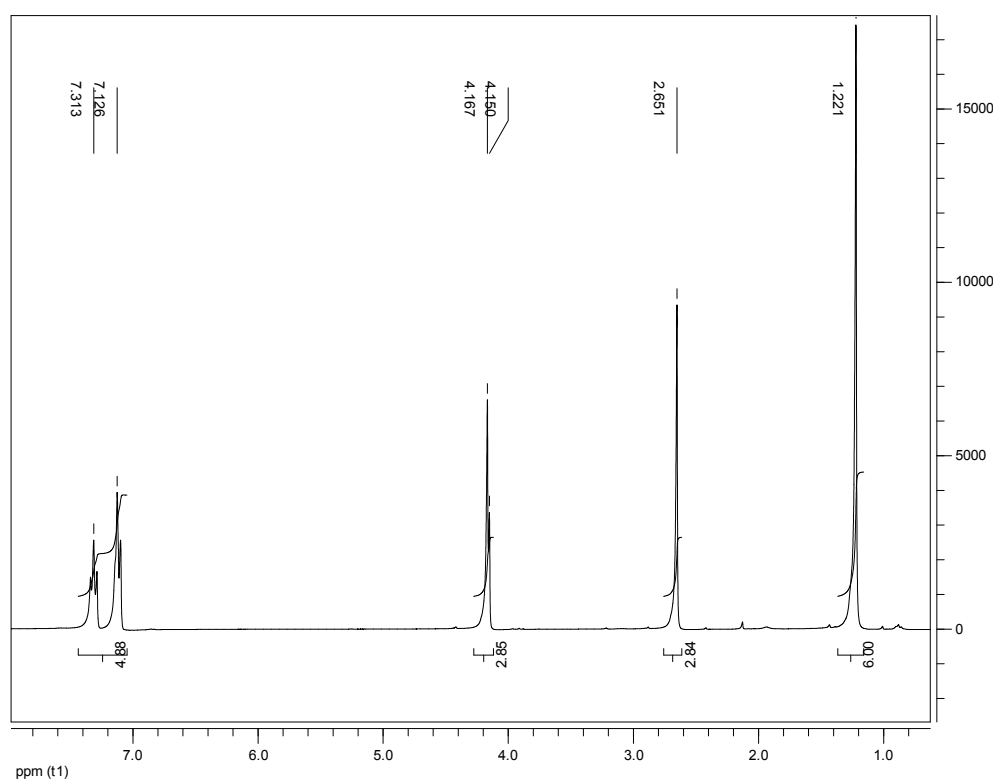


Figure 3.1 ^1H NMR of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid phenyl ester (**220**)

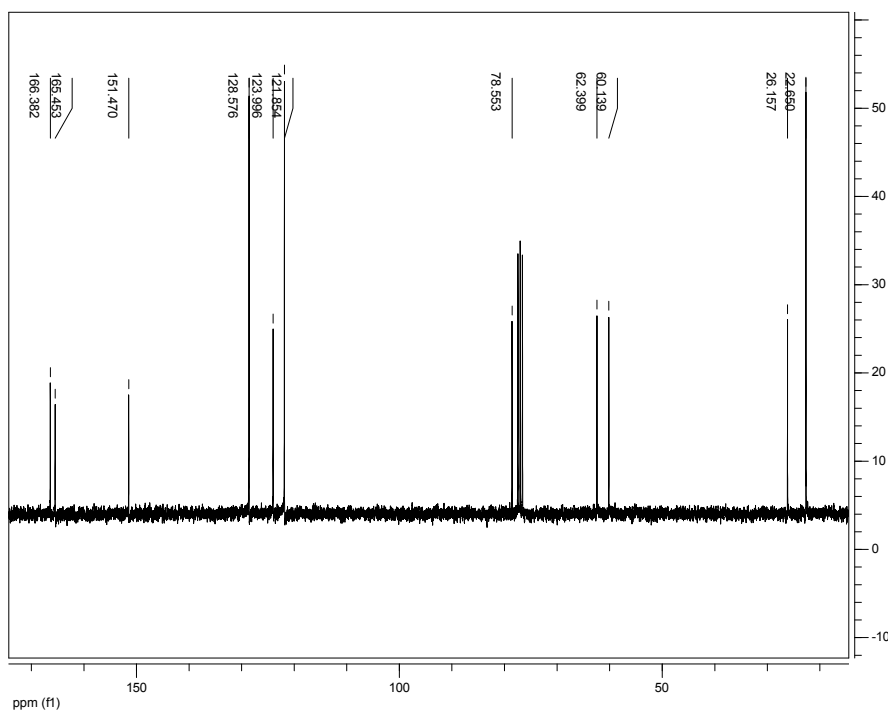


Figure 3.2 ¹³C NMR of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid phenyl ester (**220**)

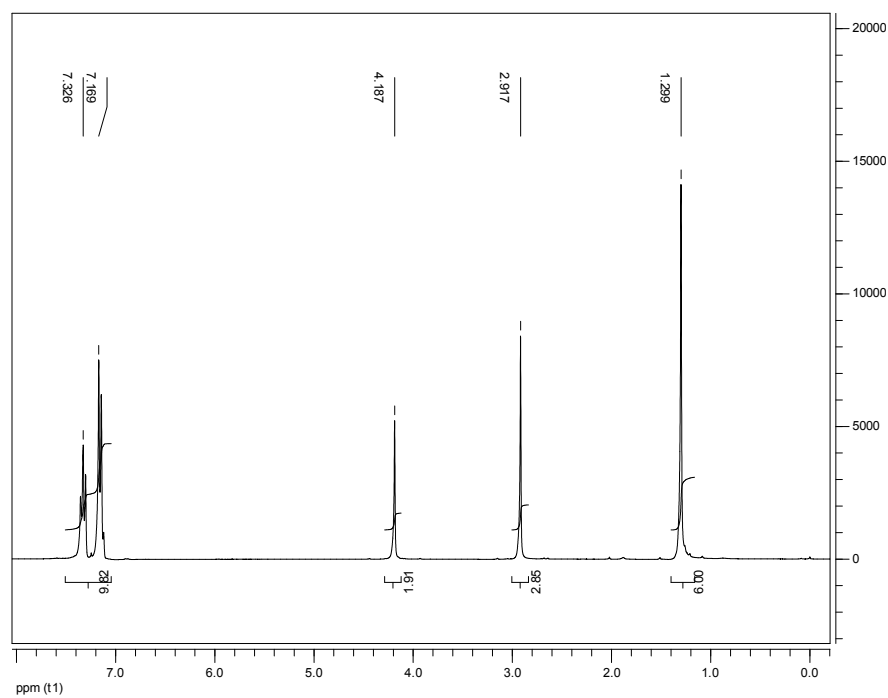


Figure 3.3 ¹H NMR of 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid diphenyl ester (**221**)

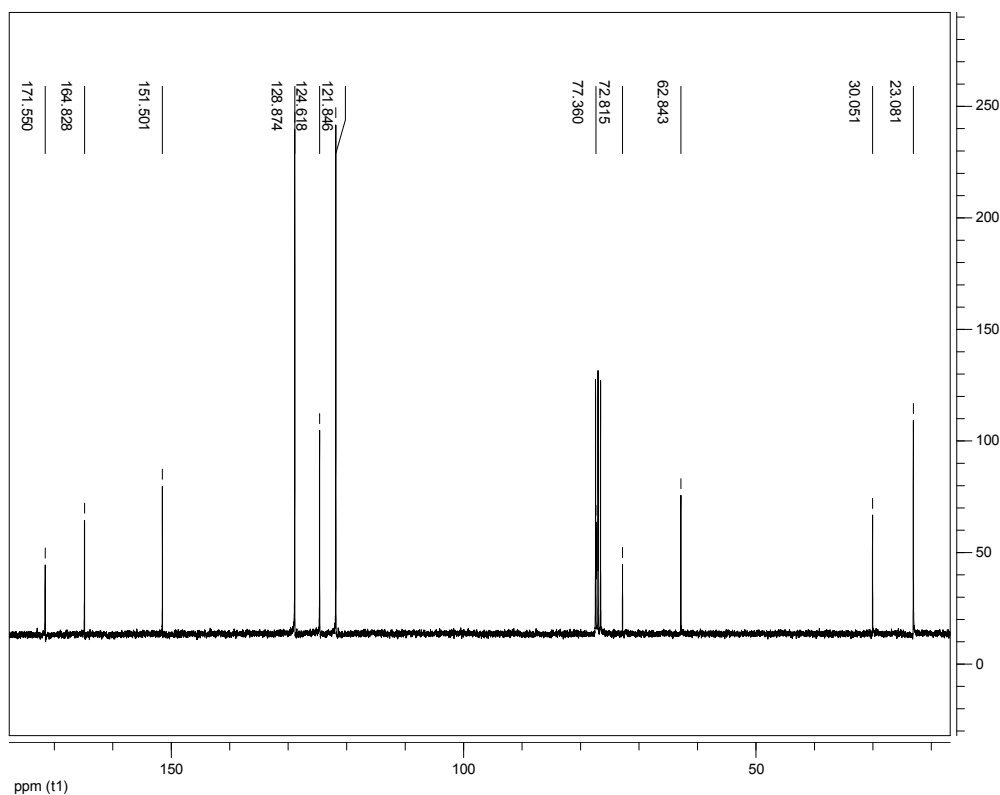


Figure 3.4 ^{13}C NMR of 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid diphenyl ester (**221**)

Preparation of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid 4-methoxyphenyl ester (**222**) and 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid bis-(4-methoxyphenyl) ester (**223**)

2,3,4,4-Tetramethyloxazolinium iodide (**182**) (1.34 g, 5.25 mmol, 1 eq.) was reacted with NaH (0.43 g, 11 mmol, 2.0 eq.) for 4.5 h in dried THF. Solid settled to the bottom and the top liquid became clear. The top layer liquid (35 mL) was taken by a syringe and added dropwise to a solution of *p*-methoxyphenyl chloroformate (0.86 g, 1.1 eq.) and 0.70 g DIPEA (1.3 eq.) in 45 mL THF, over a period of 3 h, at room temperature. The mixture was further stirred 3 h. Work up followed the procedure as described for preparation of **219**. The crude product was purified by flash column chromatography over SiO_2 gel, using acetone/hexanes (3:5 volume ratio) as the eluting

solvent. (3,4,4-Trimethyloxazolidin-2-ylidene)-acetic acid 4-methoxyphenyl ester (**222**) (0.25 g, white solid, mp 136-137 °C) was the first component to be eluted, 21 % yield. ^1H NMR (300 MHz, CDCl_3): δ 7.02 (aromatic, d, J = 7.9 Hz, 2H), 6.84 (aromatic, d, J = 7.9 Hz, 2H), 4.17 (s, $-\text{CH}_2-$, 2H), 4.13 (s, $=\text{CHCOOPh-}p\text{-OCH}_3$, 1H), 3.75 (Ph- $p\text{-OCH}_3$, 3H), 2.66 (s, $>\text{N-CH}_3$, 3H), 1.23 ($>\text{N-C(CH}_3)_2-$, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 166.2 ($-\text{COOPh-}p\text{-OCH}_3$ or $\text{N,O}>\text{C=}$), 165.8 ($\text{N,O}>\text{C=}$ or $-\text{COOPh-}p\text{-OCH}_3$), 155.9, 144.9, 122.5, 113.6 (aromatic), 78.5 ($-\text{OCH}_2-$ or $=\text{CCOOPh-}p\text{-OCH}_3$), 62.3 ($=\text{CCOOPh-}p\text{-OCH}_3$ or $-\text{OCH}_2$), 60.1 ($>\text{N-C(CH}_3)_2-$), 55.1 ($-\text{COOPh-}p\text{-OCH}_3$), 26.1 ($>\text{N-CH}_3$), 22.6 ($>\text{N-C(CH}_3)_2-$). IR (neat, cm^{-1}): 2974, 1702, 1607, 1580, 1505, 1438, 1240, 1204, 1183, 1101, 1028, 970, 847, 761, 708. mp 136-7 °C. The crystal structure of **222** is shown in Figure 3.5.

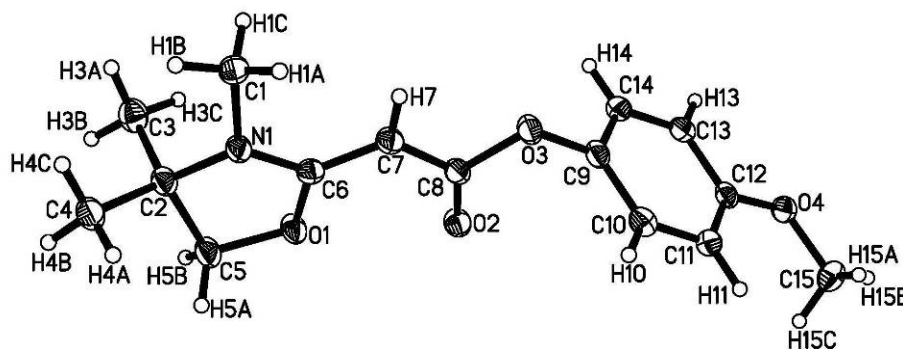


Figure 3.5 Crystal structure of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid 4-methoxyphenyl ester (**222**). CCDC: 796898

2-(3,4,4-Trimethyloxazolidin-2-ylidene)-malonic acid bis-(4-methoxyphenyl) ester (**223**) (0.26 g, white solid, mp 161-162 °C) was the second component, 14 % yield. ^1H NMR (300 MHz, CDCl_3): δ 6.80-7.15 (aromatic, 8H), 4.22 (s, $-\text{CH}_2-$, 2H), 3.76 (Ph- O-CH_3 , 6H), 2.93 (s, $>\text{N-CH}_3$, 3H), 1.34 ($>\text{N-C(CH}_3)_2-$, 6H). ^{13}C NMR (75 MHz, CDCl_3):

δ 171.4 ($-\underline{\text{C}}\text{OOPh-}p\text{-OCH}_3$), 165.3 ($\text{N,O}>\text{C=}$), 156.4, 145.0, 122.6, 114.0 (aromatic), 77.3 ($=\underline{\text{C}}(\text{COOPh-}p\text{-OCH}_3)_2$), 72.9 (s, $-\text{CH}_2-$, 2H), 62.8 ($>\text{N-}\underline{\text{C}}(\text{CH}_3)_2-$), 55.3 ($-\text{COOPhO}\underline{\text{C}}\text{H}_3$), 30.0 ($>\text{N-CH}_3$), 23.1 ($>\text{N-C}(\underline{\text{C}}\text{H}_3)_2-$). IR (neat, cm^{-1}): 2935, 1702, 1677, 1567, 1504, 1434, 1307, 1248, 1178, 1125, 1035, 1012, 862, 779 . mp 161-162 °C. The crystal structure of **223** is shown in Figure 3.6.

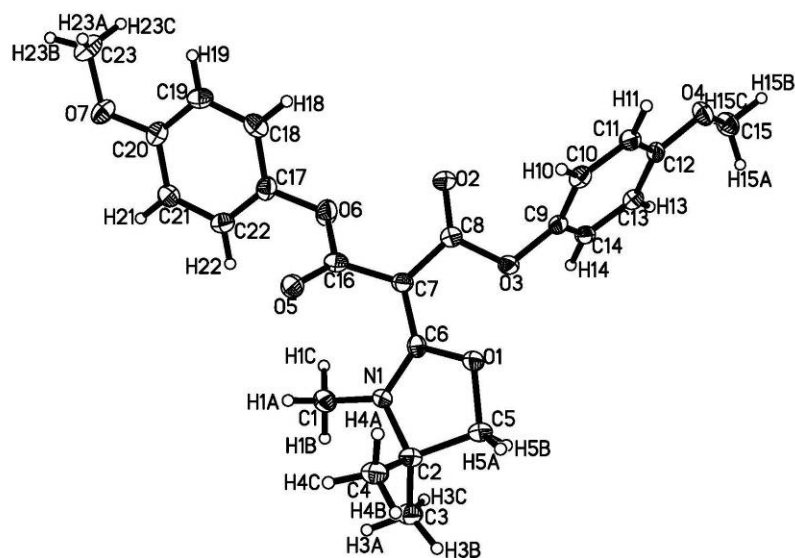


Figure 3.6 Crystal structure of 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid bis-(4-methoxyphenyl) ester (**223**). CCDC: 796895

Di-(4-methoxyphenyl) carbonate (**224**) was also obtained in 5.5 % yield. The crystal structure of **224** is shown in Figure 3.7.

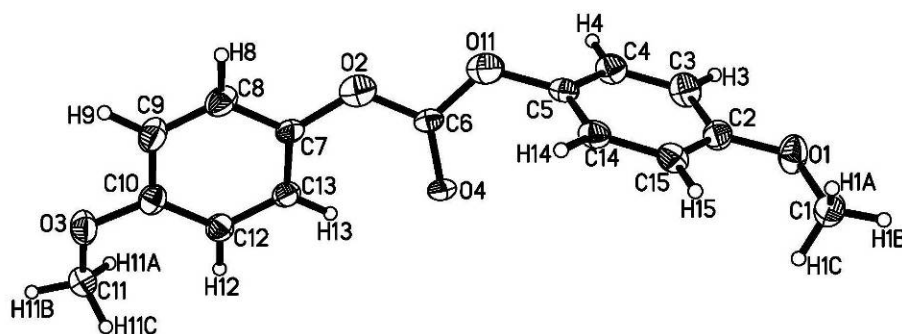


Figure 3.7 Crystal structure of di-(4-methoxyphenyl) carbonate **224**

Preparation of (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid 4-nitrophenyl ester (**225**) and 2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonic acid bis-(4-nitrophenyl) ester (**226**)

2,3,4,4-Tetramethyloxazolinium iodide (**182**) (3.28 g, 13 mmol, 1 eq.) was reacted with NaH (0.92 g, 23 mmol, 1.8 eq.) for 4 h in dried THF. Solid settled to the bottom and the top liquid became clear. The top layer liquid (40 mL) was taken by a syringe and added dropwise to the mixture of *p*-nitrophenyl chloroformate (1.53 g, 7.29 mmol, 1.12 eq.) and 1.02 g DIPEA (7.85 mmol, 1.20 eq.) in 45 mL THF, over a period of 2 h 40 min, at room temperature. The mixture was further stirred 3.5 h. Work up followed the general procedure. The crude product was purified by flash column chromatography over SiO₂ gel, using acetone/hexanes (1:2 volume ratio) as eluting solvent. (3,4,4-Trimethyloxazolidin-2-ylidene)-acetic acid 4-nitrophenyl ester (**225**) (0.040 g, white solid, mp 133-134 °C) was the first component to be eluted, yield 2.1 %. ¹H NMR (75 MHz, CDCl₃): δ 8.20 (aromatic, d, J = 9.1 Hz, 2H), 7.28 (aromatic, d, J = 9.1 Hz, 2H), 4.25 (s, -CH₂-, 2H), 4.17 (s, =CHCOOPh-*p*-NO₂, 1H), 2.75 (s, >N-CH₃, 3H), 1.31 (s, >N-C(CH₃)₂-, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 166.2 (-COOPh-*p*-NO₂ or N,O>C=), 165.8 (N,O>C= or -COOPh-*p*-NO₂), 155.9, 144.9, 122.5, 113.6 (aromatic), 78.5 (-OCH₂- or =CCOOPh-*p*-NO₂), 62.3 (=CCOOPh-*p*-NO₂ or -OCH₂), 60.1 (>N-C(CH₃)₂-), 55.1(-

COOPh-*p*-NO₂), 26.1 (>N-CH₃), 22.6 (>N-C(CH₃)₂-). IR (neat, cm⁻¹): 1722, 1577, 1501, 1483, 1328, 1230, 1099, 1030, 959, 897, 857, 826, 754, 678. 2-(3,4,4-Trimethyloxazolidin-2-ylidene)-malonic acid bis-(4-nitrophenyl) ester **226** (0.057 g, white solid, mp 227-228 °C) was the second component, yield 1.9 %. ¹H NMR (300 MHz, CDCl₃): δ 8.25 (aromatic, d, J = 9.1 Hz, 4H), 7.32 (aromatic, d, J = 9.1 Hz, 4H), 4.38 (s, -CH₂-, 2H), 3.04 (s, >N-CH₃, 3H), 1.49 (s, >N-C(CH₃)₂-, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 166.2 (-COOPh-*p*-NO₂ or N,O>C=), 165.8 (N,O>C= or -COOPh-*p*-NO₂), 155.9, 144.9, 122.5, 113.6 (aromatic), 78.5 (-OCH₂- or =CCOOPh-*p*-NO₂), 62.3 (=CCOOPh-*p*-NO₂ or -OCH₂), 60.1 (>N-C(CH₃)₂-), 55.1(-COOPh-*p*-NO₂), 26.1 (>N-CH₃), 22.6 (>N-C(CH₃)₂-). IR (neat, cm⁻¹): 1746, 1661, 1586, 1509, 1430, 1316, 1201, 1158, 1103, 1042, 942, 854, 746, 682. Di-(4-nitrophenyl) carbonate (**224**) (0.11 g, white solid, mp 130-131 °C) was also obtained, 5.5 % yield. ¹H NMR (300 MHz, CDCl₃): δ 7.51 (aromatic, d, J = 9.2 Hz, 4H), 8.35 (aromatic, d, J = 9.2 Hz, 4H). There was also a yellow solid (0.090 g) that was unidentifiable.

Reaction of cyclic ketene-*N,O*-acetal **56** with phenyl chloroformate

2,3-Dimethyloxazolinium iodide (**190**) (4.34 g, 19.1 mmol, 1 eq.) was reacted with 1.23 g NaH (30.8 mmol, 1.61 eq.) for 4 h in 65 mL dried THF. Solid settled to the bottom and the top liquid became clear. The top layer liquid (50 mL) was taken by a syringe and added dropwise to the mixture of phenyl chloroformate (1.69 g, 10.5 mmol, 1.11 eq.) and 1.49 g DIPEA (11.4 mmol, 1.21 eq.) in 38 mL THF, over a period of 3 h, at room temperature. The mixture was further stirred 4 h. A pasty product was formed in the reaction flask. Workup and purification gave unidentifiable products.

Reaction of cyclic ketene-*N,O*-acetal **56** with *p*-methoxyphenyl chloroformate

2,3-Dimethyloxazolinium iodide (**190**) (4.34 g, 19.1 mmol, 1 eq.) was reacted with 1.23 g NaH (30.8 mmol, 1.61 eq.) for 4 h in 40 mL dried THF. The top layer of the mixture (30 mL) was added dropwise to the mixture of *p*-methoxyphenyl chloroformate (1.22 g, 6.3 mmol, 1.12 eq.) and 0.94 g DIPEA (7.2 mmol, 1.3 eq.) in 32 mL THF, over a period of 3 h, at room temperature. The mixture was further stirred 4 h. Sticky paste was found at the bottom. No workup and purification were performed.

Reaction of ethyl chloroformate with *in situ* generated cyclic ketene-*N,O*-acetal **27**

The mixture of 2,3,4,4-tetramethyloxazolinium iodide (**182**) (3.65 g, 14.3 mmol, 1 eq.), 3.61 g Et₃N (35.5 mmol, 2.48 eq.), ethyl chloroformate (3.70 g, 33.1 mmol, 2.31 eq.) and 33 mL THF were stirred at room temperature for 23 h, followed by refluxing for 4.5 h. Bubbles were found to evolve at the beginning of this reaction. Workup followed the general procedure, using acetone/hexanes (2:1 volume ratio) as the eluting solvent. Chromatography gave (3,4,4-trimethyloxazolidin-2-ylidene)-acetic acid ethyl ester (**219**) (0.038 g, light yellow liquid) in yield 1.3 %.

Reaction of *p*-nitrophenyl chloroformate with *in situ* generated cyclic ketene-*N,O*-acetal **27**

The mixture of 2,3,4,4-tetramethyloxazolinium iodide (**182**) (2.64 g, 10.3 mmol, 1 eq.), 2.62 g Et₃N (25.8 mmol, 2.49 eq.), *p*-nitrophenyl chloroformate (2.40 g, 11.4 mmol, 1.10 eq.) and 68 mL THF were stirred at room temperature for 13.5 h, followed by refluxing for 9 h. Workup followed the general procedure, using ethyl acetate/hexanes (1:3 volume ratio) followed by ethyl acetate as the eluting solvent. 2-(3,4,4-

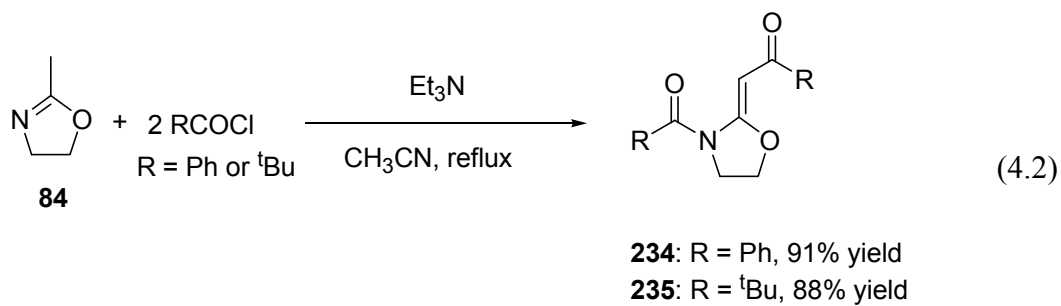
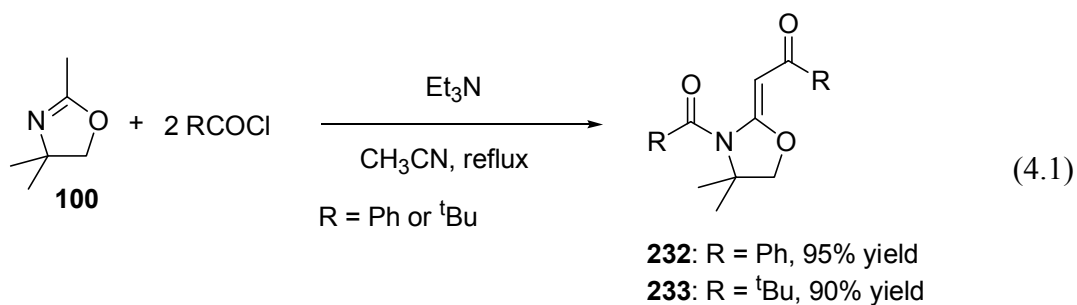
Trimethyloxazolidin-2-ylidene)-malonic acid bis-(4-nitrophenyl) ester (**226**) was generated (0.017 g, yield 0.3 %). Two other components (0.055 g and 0.075 g) were also isolated but their ^1H NMR were unidentifiable.

CHAPTER IV

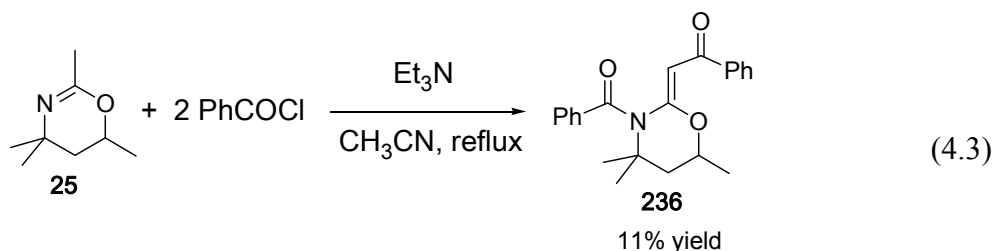
BENZOYLATION OF 2-METHYL-2-OXAZINE AND
2-METHYL-2-OXAZOLINE

Introduction

N,C-Diacylation of 2,4,4-trimethyl-2-oxazoline (**100**) by aliphatic acid chlorides without α -hydrogens and dibenzoylation by benzoyl chloride have been achieved^{14e,19} (Equation 4.1). 2-Methyl-2-oxazoline (**84**) was reported to react in a similar manner (Equation 4.2).^{14e,19}



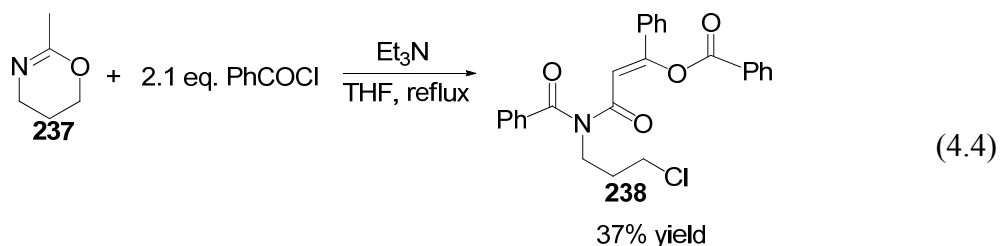
2,4,4,6-Tetramethyl-5,6-dihydro-4H-1,3-oxazine (**25**) was dibenzoylated to the corresponding six-membered cyclic ketene-*N,O*-acetal **236**, using the same chemistry⁵⁰ (Equation 4.3).



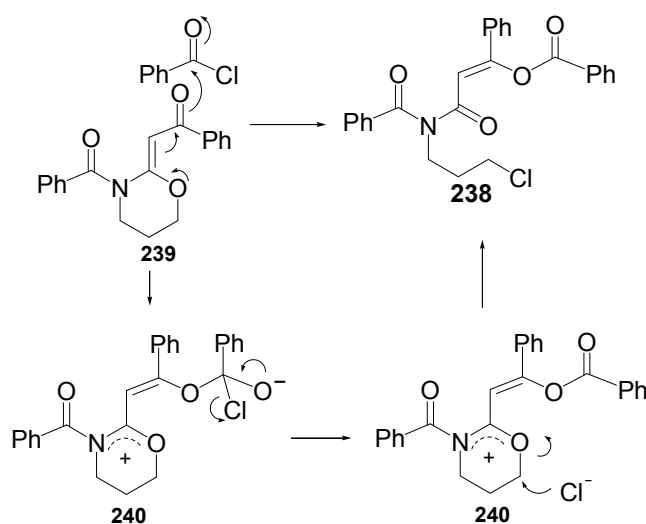
The benzoylation of 2-methyl-2-oxazine (**237**) has not been reported. It was expected that this reaction should follow the same reaction path as Equation 4.3. As will be shown in this chapter, this expectation was incorrect and a very different result was found.

Results and discussion

Benzoylation of 2-methyl-2-oxazine (**237**) was conducted using the same procedure as that for *N,C*-dibenzoylation of 2,4,4-trimethyl-2-oxazoline (**100**).^{14e,19} Unlike the conversion of **100** to **232** or **25** to **236**, the *N,C,O*-tribenzoylated, ring-opened product, 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(*Z*)-propenyl benzoate (**238**), was obtained (Equation 4.4).



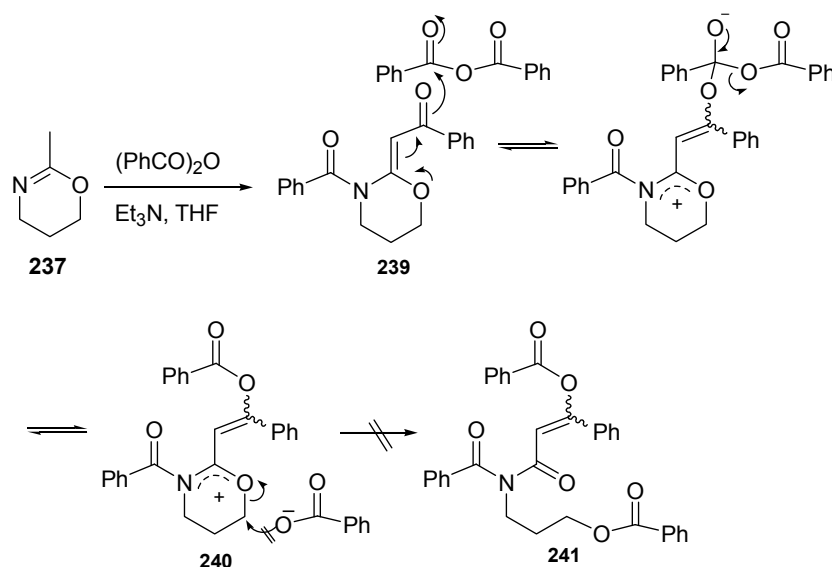
The *N,C,O*-tribenzoylated, ring-opened product **238** presumably comes from *N,C*-dibenzoylated cyclic ketene-*N,O*-acetal **239** (Scheme 4.1). The β -keto function of **239** could have been *O*-benzoylated to form cationic intermediate **240**, followed by chloride anion attack on the C6 position to open the ring. *O*-Benzoylation would be promoted by strong electron donation from the oxygen and nitrogen making the keto oxygen more negative and nucleophilic.



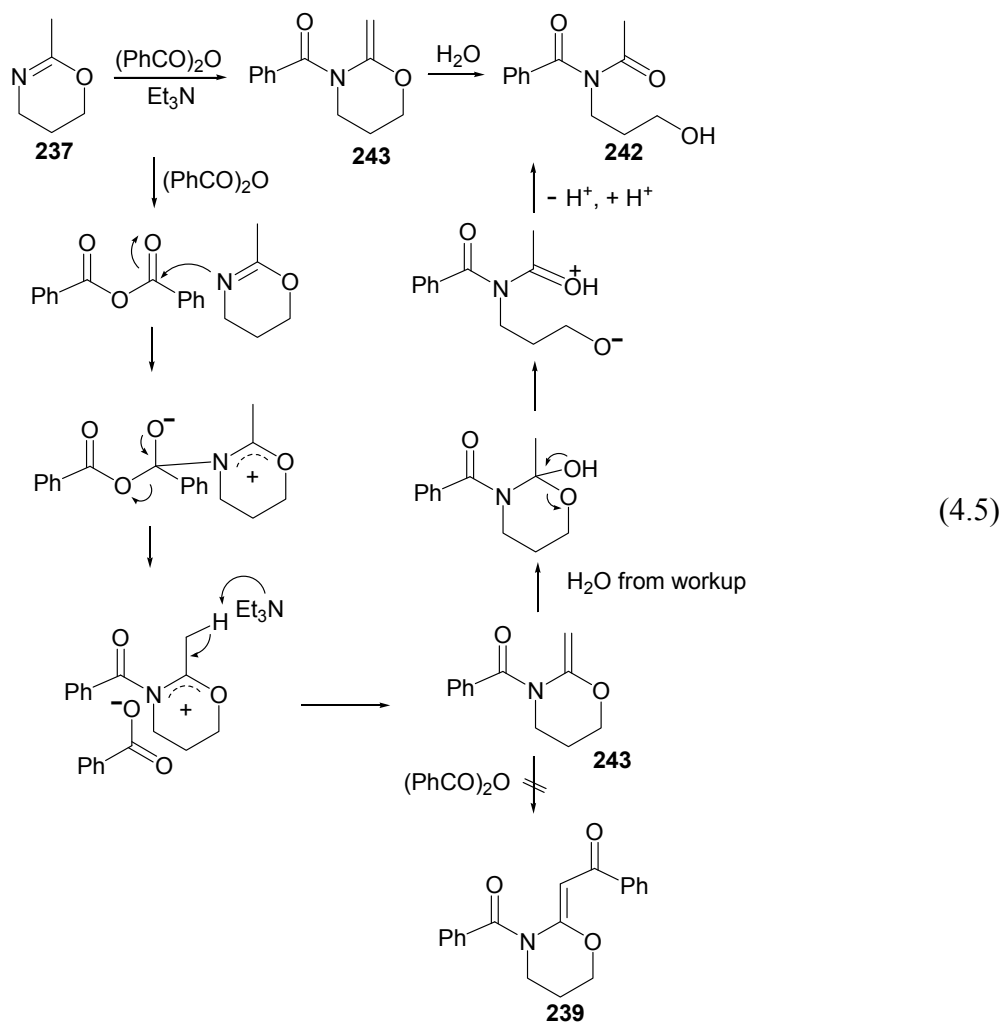
Scheme 4.1 Suggested route to *N,C,O*-tribenzoylated, ring-opened product **238** from *N,C*-dibenzoylated cyclic ketene-*N,O*-acetal **239**

As stated above, a third benzoylation at the β -keto oxygen of **239**, followed by chloride attack at the C-6 carbon of **240**, could have produced *N,C,O*-tribenzoylated, ring-opened product **238**. If benzoic anhydride was used instead of benzoyl chloride as the benzoylating reagent (Scheme 4.2), the benzoate counterion may not be nucleophilic enough to attack the C-6 carbon of **240** to open the ring. If the β -keto *O*-benzoylation occurs, the *O*-benzoylated cation intermediate **240** may simply reverse back to **239** instead of undergoing ring opening by benzoate anion to give **241**, as long as the

benzoate anion is unable to effect ring opening. Therefore, benzoylation of 2-methyl-2-oxazine (**237**) by benzoic anhydride was investigated (Equation 4.5). Neither *N,C*-dibenzoylation nor *N,C,O*-tribenzoylation followed by ring opening occurred. Instead, *N*-acetyl-*N*-(3-hydroxypropyl)-benzamide (**242**), the hydration product of *N*-benzoylated cyclic ketene-*N,O*-acetal **243**, was isolated (Equation 4.5). This indicates that benzoylation of **237** by benzoic anhydride must have stopped at **243**. During workup, **243** reacted with water and ring opens to **242**. This indicates that benzoic anhydride is too weak to benzoylate the β -carbon of **243**.

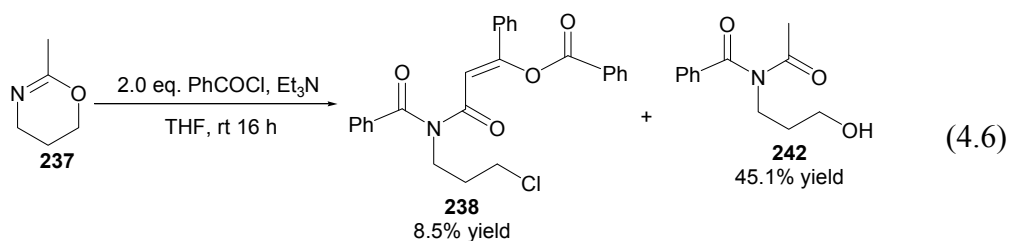


Scheme 4.2 Benzoylation of 2-methyl-2-oxazine (**237**) using benzoic anhydride may stop at the *N,C*-dibenzoylation stage



Another attempt was made to stop the benzoylation of 2-methyl-2-oxazine (**237**) at the *N,C*-dibenzoylation stage **239** (see scheme 4.2). As demonstrated in Chapter 2, when the reaction of *in situ* generated cyclic ketene-*N,O*-acetal **56** and phenyl isocyanate was conducted at room temperature, only a trace of rearranged product **195** was detected (see Chapter 2). This means that iodide, remaining in the system from the original 2,3-dimethyloxazolinium iodide salt, attacked the C-5 carbon of the 2-(3-methyloxazolidin-2-ylidene)-*N,N'*-diaryl-malonamide (**191**) at a very low rate at room temperature. Therefore, benzoylation of 2-methyl-2-oxazine (**237**) with 2.0 equivalents of benzoyl

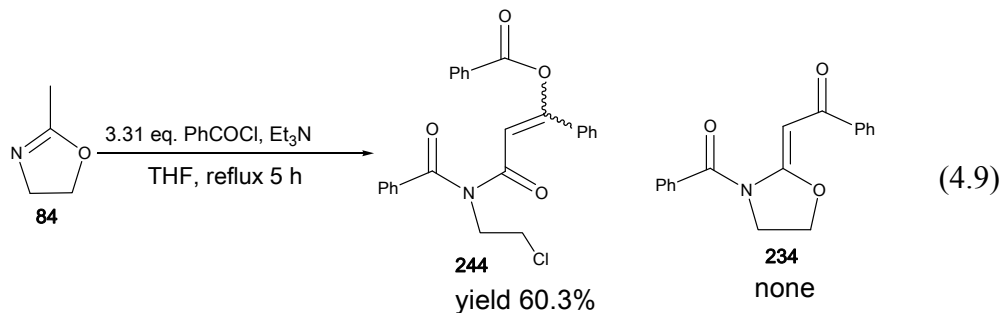
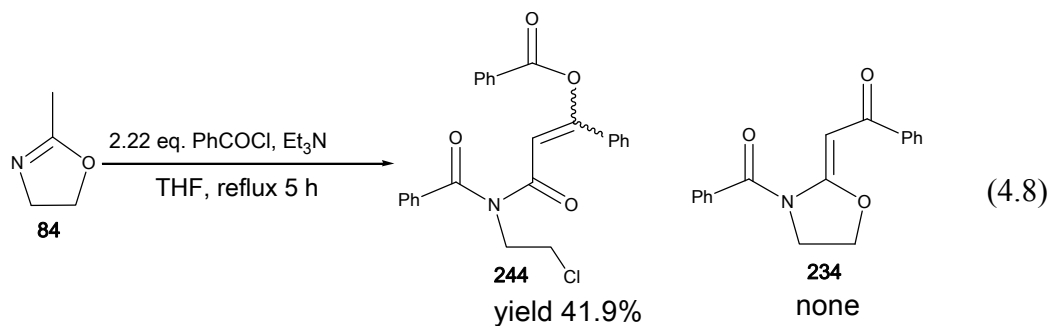
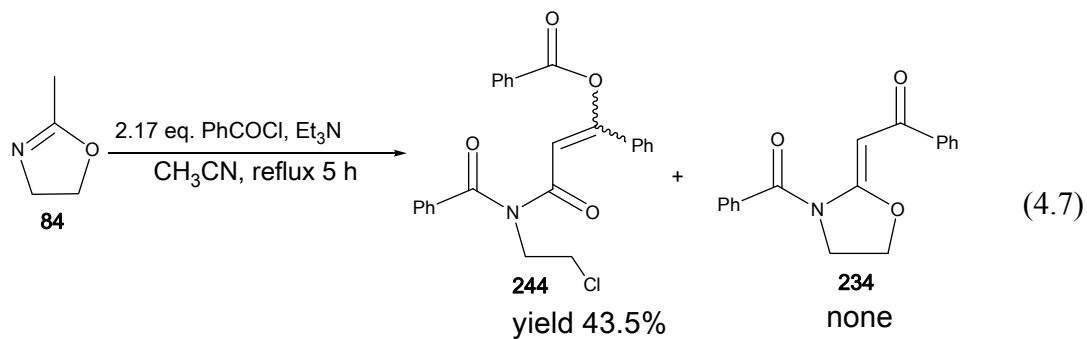
chloride in place of benzoic anhydride was conducted at room temperature (Equation 4.6) instead of 66 °C (refluxing THF). Room temperature was used to try to avoid chloride ion induced ring opening of the *N,C*-dibenzoylation product **239** that was shown in Scheme 4.1. However, the reaction still did not stop at the dibenzoylation stage. Instead, the *N,C*-dibenzoylated product was further converted to the tribenzoylated intermediate followed by chloride-induced ring opening. Only ring-opened 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(*Z*)-propenyl benzoate (**238**) and *N*-acetyl-*N*-(3-hydroxypropyl)-benzamide (**242**) were obtained.



The formation of the unexpected ring-opened *N,C,O*-tribenzoylation product **238** stands in sharp contrast with *N,C*-dibenzoylation of 2-methyl-2-oxazoline (**84**) by benzoyl chloride, which has already been reported.^{14e,19} This prompted us to revisit the benzoylation of **84**. The same procedure was employed for this reaction as reported earlier.^{14e,19} The reaction, in our hands, gave the ring-opened, *N,C,O*-tribenzoylated, product, 3-[benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (**244**), in 41.9 % yield (Equation 4.7), not the expected *N,C*-dibenzoylated product **234**. Changing the solvent from CH₃CN to THF (Equation 4.8) gave the same result in almost the same yield despite the difference in solvent boiling points.

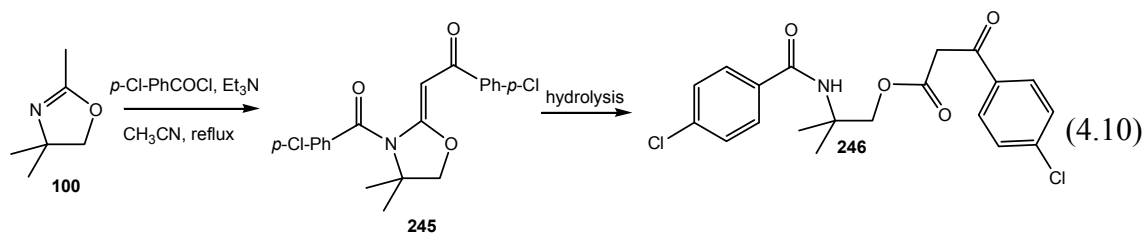
In both of the above tribenzoylation reactions, benzoyl chloride was used in lower than the stoichiometric amounts required for tribenzoylation. Therefore, 3.3 equivalents

of benzoyl chloride was used in another reaction (Equation 4.9) in refluxing THF to push up the yield of tribenzoylation product. Indeed, a 60.3 % isolated yield of **244** was achieved.

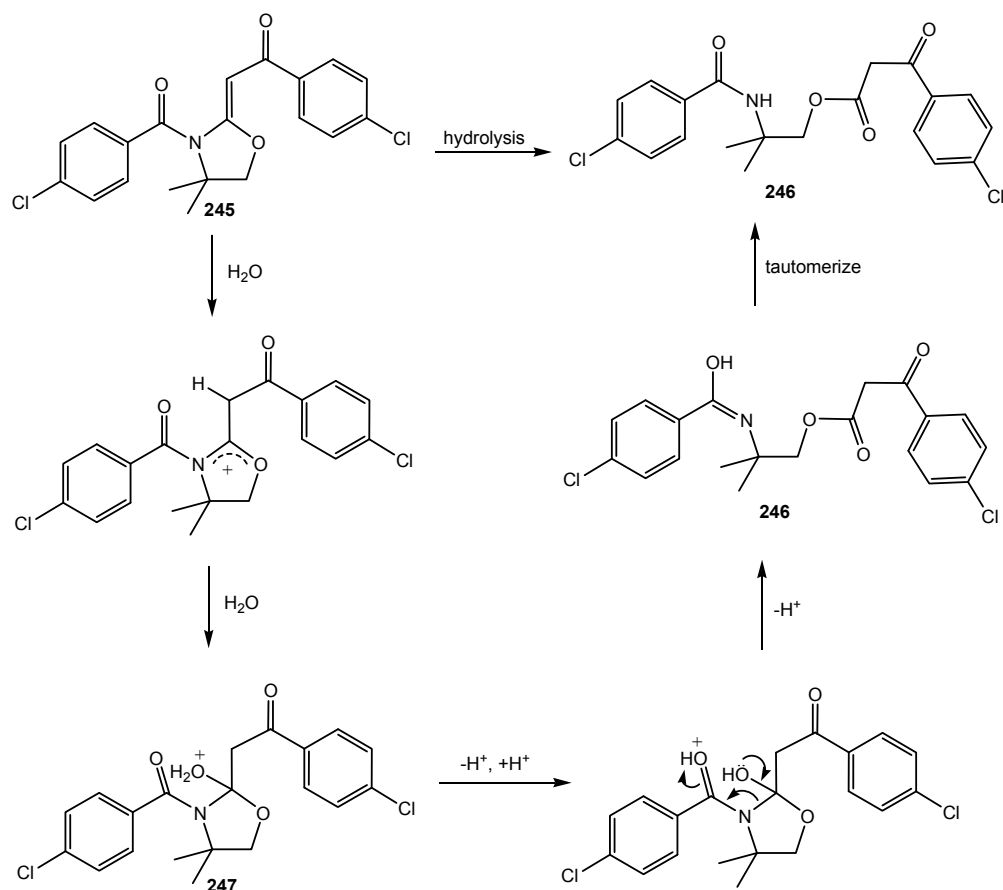


During the attempted preparation of 2-[3-(4-chlorobenzoyl)-4,4-dimethyloxazolidin-2-ylidene]-1-(4-chlorophenyl)-ethanone (**245**) from reaction of **100** with *p*-chlorobenzoyl chloride (Equation 4.10), the crude product was not immediately purified. Instead, it was stored as a DCM solution on the benchtop for four months. Upon chromatography, **245** was not isolated from this crude product. Instead, 3-(4-

chlorophenyl)-3-oxopropionic acid 2-(4-chlorobenzoylamino)-2-methyl-propyl ester (**246**) was isolated in 37.8 % yield. This is a ring-opened product, expected from the hydrolysis of the *N,C*-di(*p*-chlorobenzoylated) cyclic ketene-*N,O*-acetal **245**. Apparently, during the long storage time (four months) after the crude product was worked up, hydrolysis occurred to **245** (Equation 4.10). Thus, it appears that **245** should be available via this route if an immediate isolation of product was conducted following the reaction. Such a workup should involve a basic pH if water washing is used, because protonation at the β -carbon of **245** generates a very stable oxazolinium cation which is attacked by water at the ring carbon.



The mechanism proposed for hydrolysis of **245** (Scheme 4.3) involves water addition across the exocyclic carbon-carbon double bond to form adduct **247**. Proton transfer to the oxygen of the amide moiety makes it a good leaving group. Ring opening gives **246**.



Scheme 4.3 Hydrolysis of 2-[3-(4-chlorobenzoyl)-4,4-dimethyloxazolidin-2-ylidene]-1-(4-chlorophenyl)-ethanone (**245**)

In conclusion, the benzylation of 2-methyl-2-oxazine (**237**) and 2-methyl-2-oxazoline (**84**) gave ring-opened *N,C,O*-tribenzoylation products. This stands in sharp contrast to the benzoylations of 2,4,4,6-tetramethyl-5,6-dihydro-4H-1,3-oxazine (**25**) and 2,4,4-trimethyl-2-oxazoline (**100**), which gave ring-retained *N,C*-dibenzoylation products **236** and **232**, respectively. The methyl group at C-6 of **236** and the two methyl groups at C-4 of **232** hinder the attack of chloride anion on the methylene carbon next to the ring oxygen. This steric effect has been demonstrated in Chapters 2 and 3.

Experimental

Preparation of 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(Z)-propenyl benzoate (**238**) by benzoylation of 2-methyl-2-oxazine (**237**) in refluxing THF

2-Methyl-2-oxazine (**237**) (1.64 g, 16.6 mmol, 1 eq.) was placed in a 100 mL flask, followed by dried THF (92 mL) and Et₃N (4.05 g, 39.8 mmol, 2.40 eq.). The solution was cooled by an external ice bath. Benzoyl chloride (5.01 g, 35.3 mmol, 2.13 eq.) was added dropwise over 16 min. The resulting suspension was allowed 20 min to warm to room temperature, followed by refluxing for 4.5 h under nitrogen. Rotary evaporation removed the solvent. Dichloromethane (23 mL) and saturated NaHCO₃ (38 mL) were added to the residue and the mixture was stirred for 10 min. The organic layer was further washed with brine (2 x 32 mL), and dried over anhydrous Na₂SO₄. After concentrating by rotary evaporation, the crude product was purified by flash column chromatography over silica gel, using mixed ethyl acetate/hexanes (1: 3.5 volume ratio) as the eluting solvent. A white solid, 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(Z)-propenyl benzoate (**238**) (2.73 g, 6.1 mmol) was obtained, yield 36.8 % (based on 2-methyl-2-oxazine **237**). mp 103-105 °C. ¹H NMR (300 MHz, CDCl₃, Figure 4.1): δ 7.05-8.35 (m, aromatic H, 15H), 6.10 (s, =CH(Ph)-O-, 1H), 4.00 (t, *J* = 6.7 Hz, -CH₂-Cl, 2H), 3.54 (t, *J* = 6.4 Hz, >N-CH₂-, 2H), 2.12 (m, -CH₂-CH₂-CH₂-, 2H). ¹³C NMR (75 MHz, CDCl₃, Figure 4.2): δ 173.2 (PhCO- or OCOPh or >NCOCH= or =C(Ph)OCOPh), 166.3 (PhCO- or OCOPh or >NCOCH= or =C(Ph)OCOPh), 163.4 (PhCO- or OCOPh or >NCOCH= or =C(Ph)OCOPh), 155.5 (PhCO- or OCOPh or >NCOCH= or =C(Ph)OCOPh), 136.0 (aromatic), 133.8(aromatic), 133.3(aromatic), 132.6(aromatic), 130.7(aromatic), 130.2(aromatic), 128.9(aromatic), 128.8(aromatic),

128.7(aromatic), 128.6(aromatic), 128.5(aromatic), 125.6(aromatic), 110.6(=CH(Ph)-O-), 43.4(>N-CH₂- or -CH₂-Cl), 42.3 (>N-CH₂- or -CH₂-Cl), 31.6 (-CH₂-CH₂-CH₂-). IR (neat, cm⁻¹): 3055, 2956, 1742, 1696, 1630, 1233, 1171, 1124, 1062, 1023, 764, 720, 691. The crystal structure of **238** is shown in Figure 4.3.

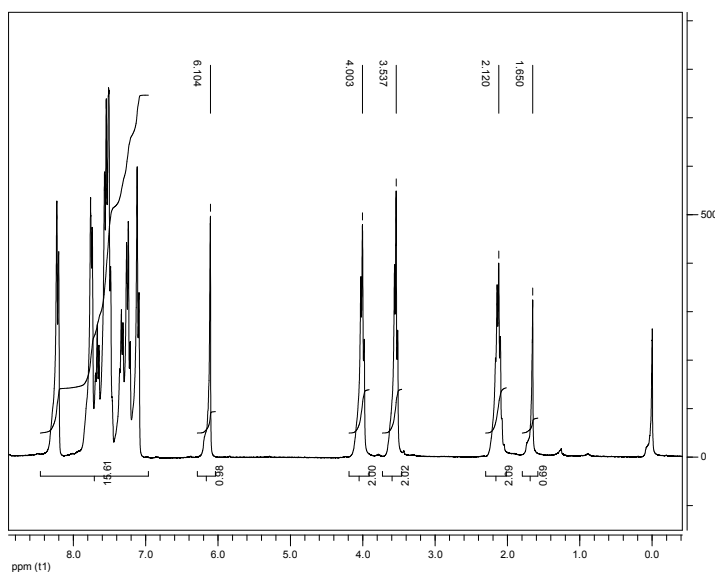


Figure 4.1 ¹H NMR of 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(Z)-propenyl benzoate (**238**)

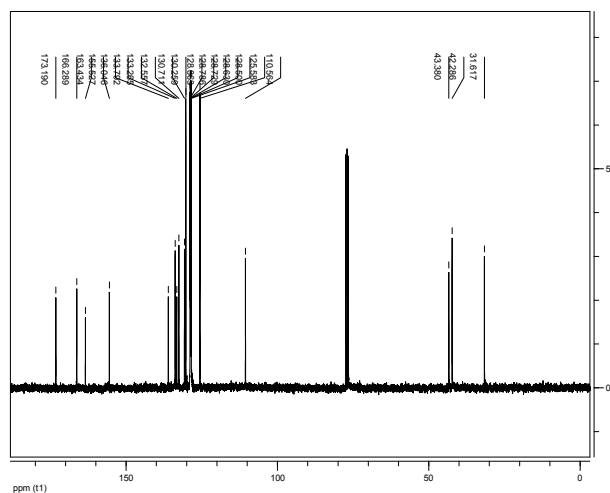


Figure 4.2 ¹³C NMR of 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(Z)-propenyl benzoate (**238**)

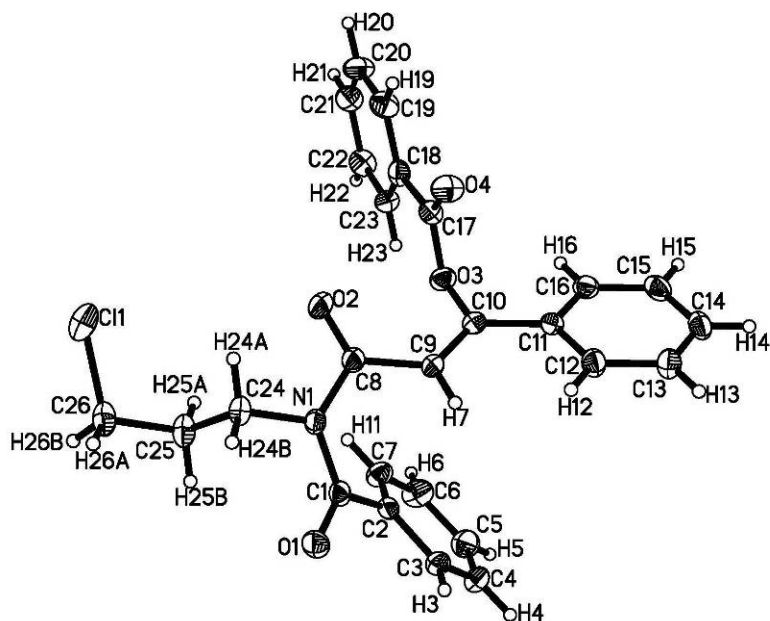


Figure 4.3 Crystal structure of 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(Z)-propenyl benzoate (**238**). CCDC 796896

Preparation of *N*-acetyl-*N*-(3-hydroxypropyl)-benzamide (**242**) by benzoylation of 2-methyl-2-oxazine (**237**) with benzoic anhydride

2-Methyl-2-oxazine (**237**) (1.17 g, 11.8 mmol, 1 eq.) was placed in a 100 mL flask, followed by dried THF (44 mL) and Et₃N (2.82 g, 27.7 mmol, 2.35 eq.). The solution was cooled by an external ice bath. Benzoic anhydride (6.12 g, 26.5 mmol, 2.24 eq.), diluted in 15 mL dried THF, was added dropwise over 18 min. The resulting suspension was allowed 13 min to warm to room temperature, followed by refluxing for 5 h under nitrogen. A clear solution was obtained. Rotary evaporation was used to remove the solvent. Dichloromethane (19 mL) and saturated NaHCO₃ (47 mL) were added to the residue and the mixture was stirred for 10 min. The organic layer was washed further with brine (41 mL), and dried over anhydrous Na₂SO₄. After concentrating by rotary evaporation, the crude product was purified by flash column

chromatography over silica gel, using mixed acetone/hexanes (1: 2 volume ratio) as the eluting solvent. *N*-Acetyl-*N*-(3-hydroxypropyl)-benzamide, **242** (light yellow liquid, 1.18 g, 5.3 mmol) was obtained upon solvent removal, yield 45.2 % (based on 2-methyl-2-oxazine **237**). ^1H NMR (300 MHz, CDCl_3 , Figure 4.4): δ 7.28-7.90 (m, aromatic H, 5H), 7.93 (-CH OH , 1H), 4.11 (t, J = 5.5 Hz, -CH OH , 2H), 3.47 (m, >N-CH $_2$ -, 2H), 1.98 (s, CH $_3$ C=O, 3H), 1.91 (m, -CH $_2$ -CH $_2$ -CH $_2$ -, 2H). ^{13}C NMR (75 MHz, CDCl_3 , Figure 4.5): δ 170.6 (PhCO- or CH $_3$ CO), 167.4 (PhCO- or CH $_3$ CO), 133.9 (aromatic), 130.7 (aromatic), 127.8 (aromatic), 126.5 (aromatic), 61.6(-CH OH), 36.3 (>N-CH $_2$ -), 28.0 (-CH $_2$ -CH $_2$ -CH $_2$ -), 20.27 and 20.23 (CH $_3$ CO). IR (neat, cm^{-1}): 3321, 1735, 1636, 1578, 1534, 1490, 1365, 1236, 1046, 693.

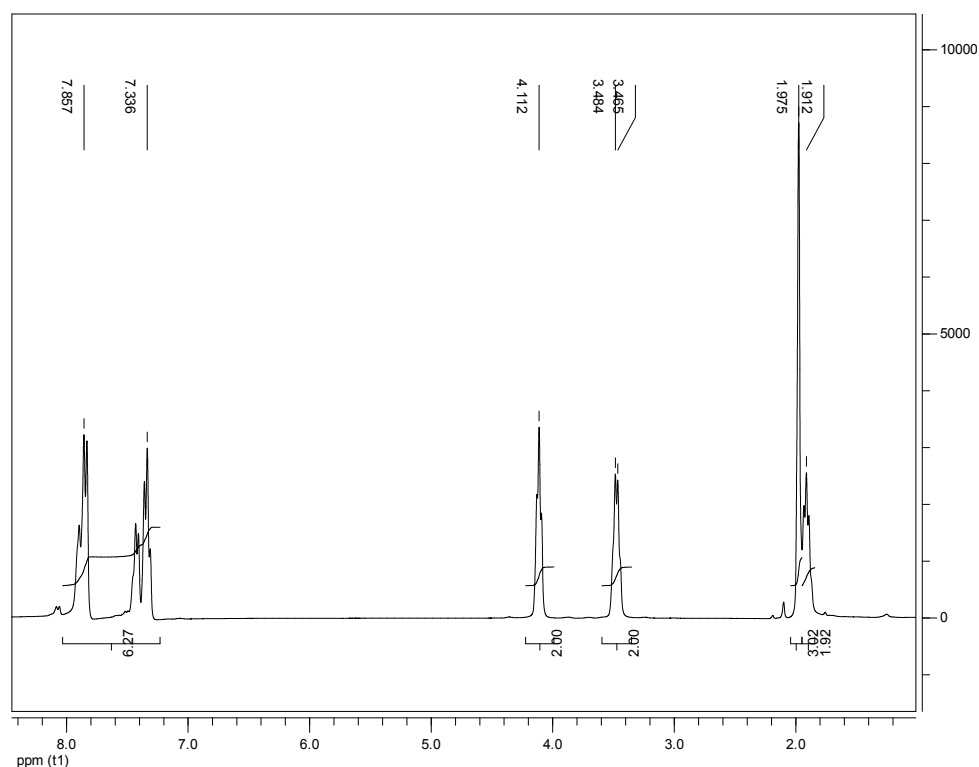


Figure 4.4 ^1H NMR of *N*-acetyl-*N*-(3-hydroxypropyl)-benzamide (**242**)

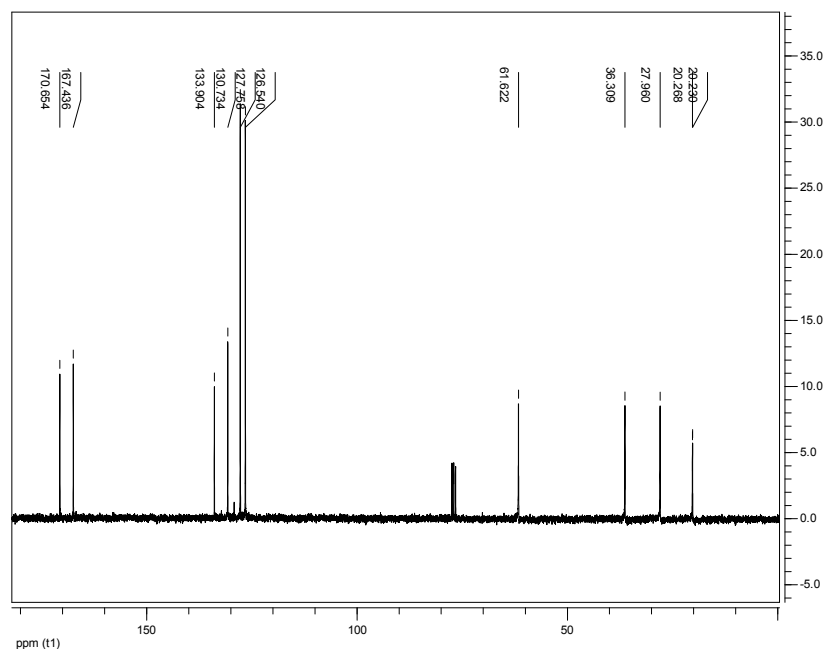


Figure 4.5 ^{13}C NMR of *N*-acetyl-*N*-(3-hydroxypropyl)-benzamide (**242**)

Attempted preparation of 2-(3-benzoyl-[1,3]oxazinan-2-ylidene)-1-phenylethanone (**239**) by benzoylation of 2-methyl-2-oxazine (**237**) at room temperature

2-Methyl-2-oxazine (**237**) (1.04 g, 10.5 mmol, 1 eq.) was placed in a 100 mL flask, followed by dried THF (71 mL) and Et_3N (2.60 g, 25.6 mmol, 2.43 eq.). The solution was cooled by an external ice bath. Benzoyl chloride (3.00 g, 21.1 mmol, 2.01 eq.), was added dropwise over 16 min. The resulting white suspension was stirred 2 h at ice bath temperature, followed by 14 h at room temperature under nitrogen. A yellow suspension was obtained. Rotary evaporation was used to remove the solvent. Then dichloromethane (17 mL) and deionized water (25 mL) were added to the residue. This mixture was stirred for 10 min. The organic layer was separated and washed further with deionized water (25 mL), and dried over anhydrous Na_2SO_4 . After concentrating by rotary evaporation, the crude product was purified by flash column chromatography over silica gel, using mixed acetone/hexanes (1:3 then 1: 2 volume ratio) as the eluting

solvent. The first product that eluted was a white solid (0.40 g), and its ^1H NMR, ^{13}C NMR, IR and melting point were identical to those of 3-[benzoyl-(3-chloropropyl)-amino]-3-oxo-1-phenyl-(*Z*)-propenyl benzoate (**238**). Yield 8.5 %. The second product eluted is a light yellow liquid (1.04 g), and was identified to be *N*-acetyl-*N*-(3-hydroxypropyl)-benzamide (**242**). Yield 44.8 %. The expected *N,C*-dibenzoylated compound was not obtained.

Preparation of 3-[benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (**244**) by benzoylation of 2-methyl-2-oxazoline (**84**) in THF

2-Methyl-2-oxazoline (**84**) (6.65 g, 77.3 mmol, 1 eq.) was placed in a 200 mL flask, followed by dried THF (154 mL) and Et_3N (20.22 g, 198.8 mmol, 2.57 eq.). The solution was cooled by an external ice bath. Benzoyl chloride (24.43 g, 172.0 mmol, 2.22 eq.), diluted in 21 mL dried THF, was added dropwise over 27 min. The resulting suspension was allowed 25 min to warm to room temperature, followed by refluxing for 5 h under nitrogen. A yellow suspension was obtained. Solvent was removed by rotary evaporation. Dichloromethane (68 mL) and saturated NaHCO_3 (113 mL) were added to the residue and the mixture was stirred for 10 min. The organic layer was washed further with brine (2 x 81 mL), and dried over anhydrous Na_2SO_4 . After concentrating by rotary evaporation, the crude product was purified by flash column chromatography over silica gel, using mixed ethyl acetate/hexanes (1:3 volume ratio) as the eluting solvent. 3-[Benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (**244**) (white solid, mp 123-124 °C, 14.05 g, 32.4 mmol) was obtained, yield 41.9 % (based on 2-methyl-2-oxazoline (**84**)). ^1H NMR (300 MHz, CDCl_3 , Figure 4.6): δ 7.05-8.25 (m, aromatic H, 15H), 6.12 (s, $=\text{CH}(\text{Ph})\text{-O-}$, 1H), 4.23 (t, $J = 4.5$ Hz, $-\text{CH}_2\text{-Cl}$, 2H), 3.77 (t, $J = 4.5$ Hz,

>N-CH₂-, 2H). ¹³C NMR (75 MHz, CDCl₃, Figure 4.7): δ 173.2 (PhCO- or OCOPh or >NCOCH= or =C(Ph)OCOPh), 166.3 (PhCO- or OCOPh or >NCOCH= or =C(Ph)OCOPh), 163.5 (PhCO- or OCOPh or >NCOCH= or =C(Ph)OCOPh), 156.1 (PhCO- or OCOPh or >NCOCH= or =C(Ph)OCOPh), 135.9 (aromatic), 133.9 (aromatic), 133.3 (aromatic), 132.8 (aromatic), 130.8 (aromatic), 130.3 (aromatic), 129.2 (aromatic), 128.9 (aromatic), 128.8 (aromatic), 128.7 (aromatic), 128.6 (aromatic), 125.7 (aromatic), 110.2 (=CH(Ph)-O-), 46.7 (>N-CH₂- or -CH₂-Cl), 42.1 (>N-CH₂- or -CH₂-Cl). IR (neat, cm⁻¹): 1743, 1696, 1672, 1625, 1226, 1174, 1139, 1086, 765, 693. mp 123-124 °C.

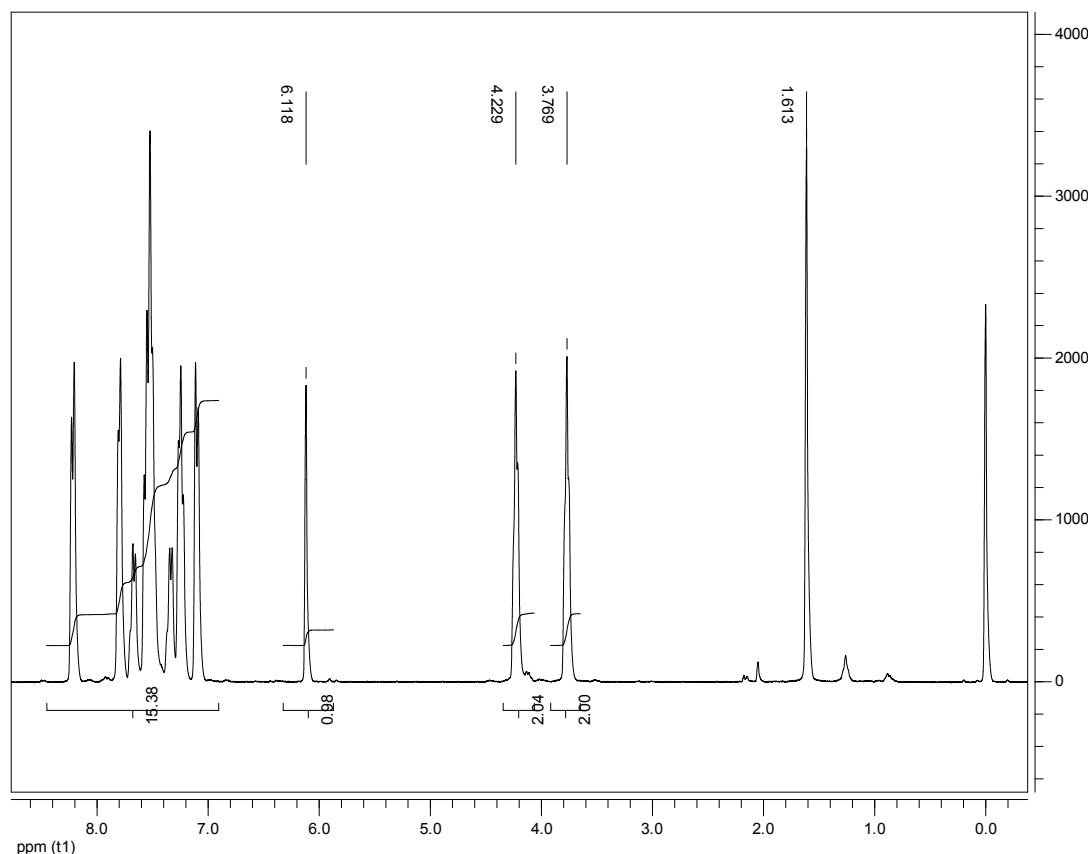


Figure 4.6 ¹H NMR of 3-[benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (**244**)

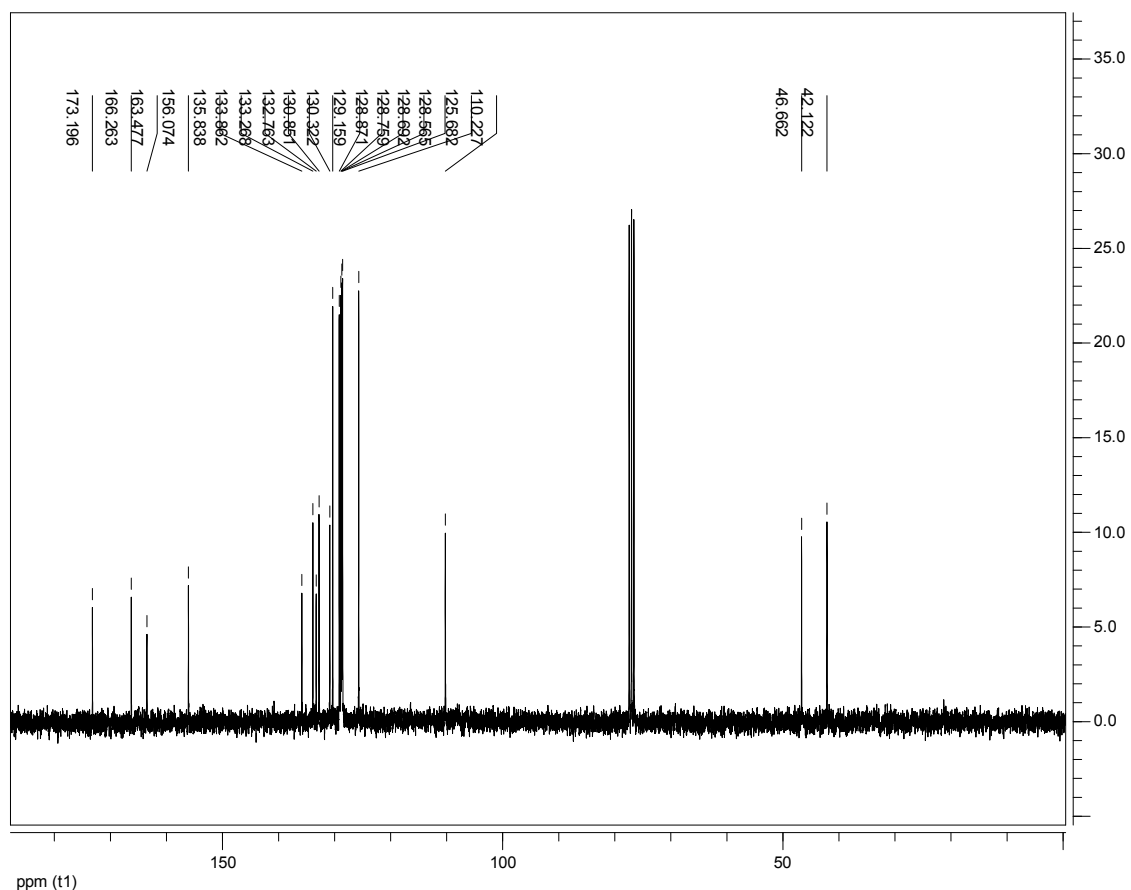


Figure 4.7 ^{13}C NMR of 3-[benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (**244**)

Preparation of 3-[benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (**244**) by benzoylation of 2-methyl-2-oxazoline (**84**) with 3.3 equivalents of benzoyl chloride in THF

2-Methyl-2-oxazoline (**84**) (5.49 g, 63.8 mmol, 1 eq.) was reacted with benzoyl chloride (30.02 g, 211.4 mmol, 3.31 eq.), in the presence of Et_3N (17.45 g, 171.6 mmol, 2.69 eq.), in dried THF (129 mL). The reaction, workup and purification procedures followed the benzoylation of **84** with benzoyl chloride in THF, as stated above. 3-[Benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (**244**) (white solid, mp 123-124 $^\circ\text{C}$, 18.42 g, 42.48 mmol) was obtained, yield 60.3 %.

Preparation of 3-(4-chlorophenyl)-3-oxopropionic acid 2-(4-chlorobenzoylamino)-2-methyl-propyl ester (**246**)

2,4,4-Trimethyl-2-oxazoline (1.708 g, 14.95 mmol, 1 eq.) was placed into a 100 mL flask, followed by dried THF (37 mL), Et₃N (3.881 g, 38.16 mmol, 2.55 eq.). At ice bath temperature, *p*-chlorobenzoyl chloride (5.702 g, 32.26 mmol, 2.16 eq.) was added dropwise over 11 min. The resulting suspension was allowed 20 min to warm to room temperature, followed by refluxing for 5 h under nitrogen. Rotary evaporation was used to remove the solvent. Then dichloromethane (23 mL) and deionized water (30 mL) were added to the residue and the mixture was stirred for 10 min. The organic layer, which was yellow milk like, was washed further with brine (24 mL) and it remained milky. Upon rotary evaporation to remove DCM, chloroform (20 mL) was added and the mixture stirred, but it remained milky. After further washing with 24 mL brine, the organic layer was dried over Na₂SO₄, and set on benchtop for four months. The solvent evaporated naturally even though the container was stoppered. Four months later, the remaining solid was washed with DCM, and the organic layer was concentrated by rotary evaporation. The mixture was purified by flash column chromatography over silica gel, using mixed ethyl acetate/hexanes (1: 3 volume ratio) as the eluting solvent. 3-(4-Chlorophenyl)-3-oxopropionic acid 2-(4-chlorobenzoylamino)-2-methyl-propyl ester (**246**) (2.201 g, 5.64 mmol) was obtained in yield 37.8 %. Yellow crystals, mp 101-102 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.28-7.83 (m, aromatic H, 8H), 6.40 (s, N,O>C=CH-, 1H), 4.38 (s, -C(=O)CH₂C(=O)-, 2H), 4.02 (s, -O-CH₂-, 2H), 1.46 (s, >C(CH₃)₂, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 191.3 (CH₂-C(=O)-C₆H₄-*p*-Cl), 167.2 (-NH-C(=O)-C₆H₄-*p*-Cl or -O-C(=O)CH₂-), 165.9 (-NH-C(=O)-C₆H₄-*p*-Cl or -O-C(=O)CH₂-), 140.4 (aromatic C), 137.2

(aromatic C), 133.8 (aromatic C), 133.3 (aromatic C), 129.6 (aromatic C), 129.0 (aromatic C), 128.4 (aromatic C), 128.2 (aromatic C), 87.0 (N,O>C=CH-), 70.0 (>N-C(CH₃)₂), 53.8 (-O-CH₂-) 45.7 (-C(=O)CH₂C(=O)-) and 23.7 (>C(CH₃)₂).IR (neat, cm⁻¹): 3390, 2967, 2930, 1736, 1652, 1586, 1527, 1279, 1158, 1091, 993, 828, 760.

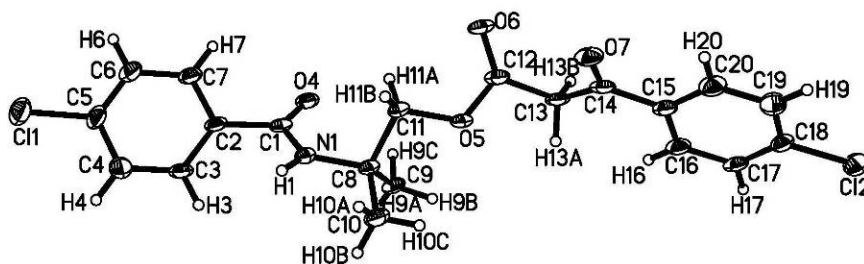


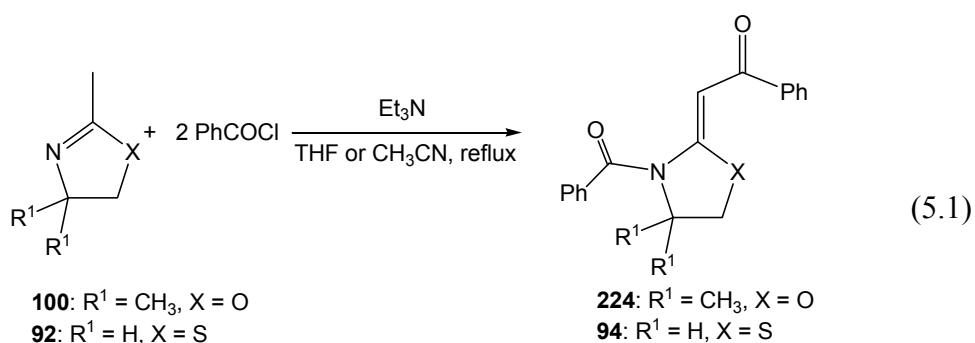
Figure 4.8 The crystal structure of 3-(4-chlorophenyl)-3-oxopropionic acid 2-(4-chlorobenzoylamino)-2-methyl-propyl ester (**246**)

CHAPTER V

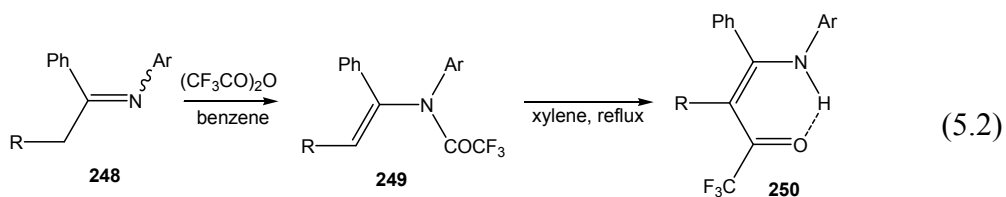
TRIFLUOROACETYLATION OF 2-METHYL-2-OXAZOLINES, 2-METHYL-2-THIAZOLINE AND 2-METHYL-2-OXAZINE

Introduction

2,4,4-Trimethyl-2-oxazoline (**100**) and 2-methyl-2-thiazoline (**92**) reacted with benzoyl chloride in the presence of base to form *N,C*-dibenzoylated cyclic ketene-*N,O*-acetals **224** and **94**, respectively^{14e,19} (Equation 5.1).



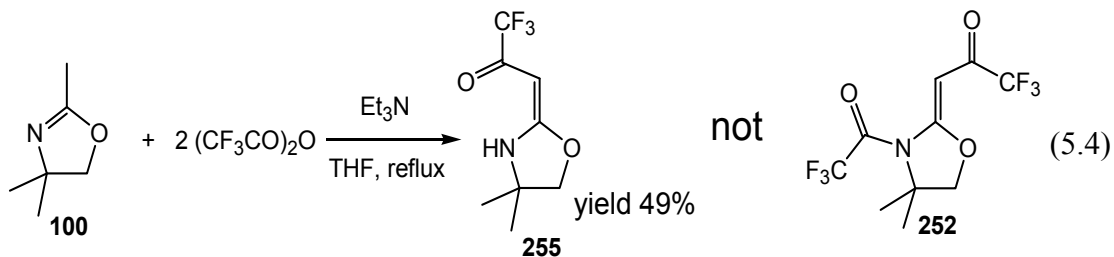
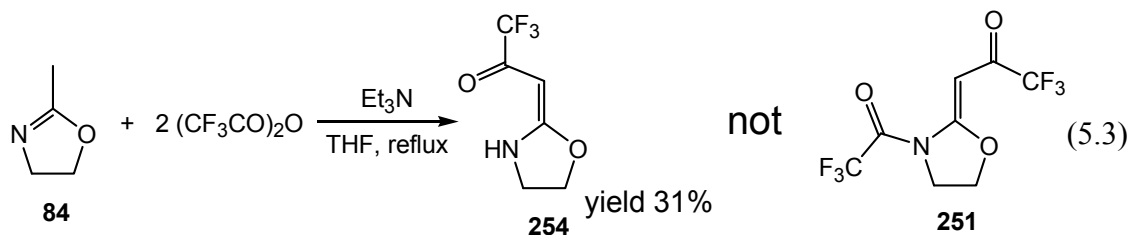
Their trifluoroacetylation, however, has not been reported. Trifluoroacetylation via trifluoroacetic anhydride is an important means to introduce trifluoroacetyl functions. Trifluoroacetic anhydride is a strong electrophile and may exhibit a different behavior than benzoyl chloride when it reacts with 2-methyl-2-oxazolines or 2-methyl-2-thiazolines. The reaction of *N*-(α -methylbenzylidene) aniline (**248**), an imine, with trifluoroacetic anhydride gave the *N*-trifluoroacetylation product **249**. The latter underwent a thermal trifluoroacetic migration from nitrogen to carbon, upon refluxing in xylene, to give **250**⁵¹ (Equation 5.2).

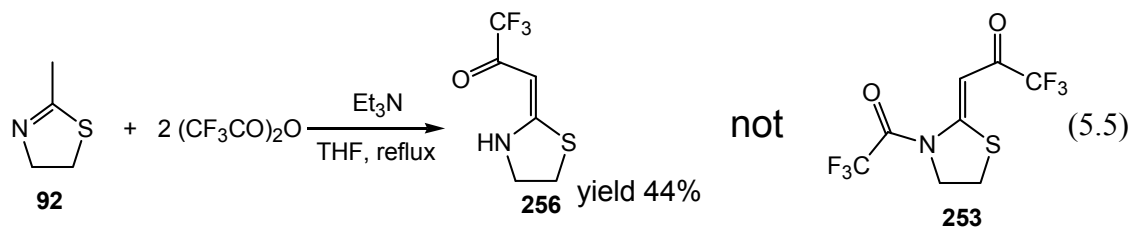


Will trifluoroacetylations of 2,4,4-trimethyl-2-oxazoline (**100**) and 2-methyl-2-thiazoline (**92**) follow the same route as their corresponding benzoylation reactions to give the *N,C*-dibenzoylated cyclic ketene-*N,O*-acetals? To answer this question, **100** and **92** were reacted with trifluoroacetic anhydride using the procedure^{14e,19} that was employed for their benzoylation. Trifluoroacetylations of 2-methyl-2-oxazoline (**84**) and 2-methyl-2-oxazine (**237**) were also explored.

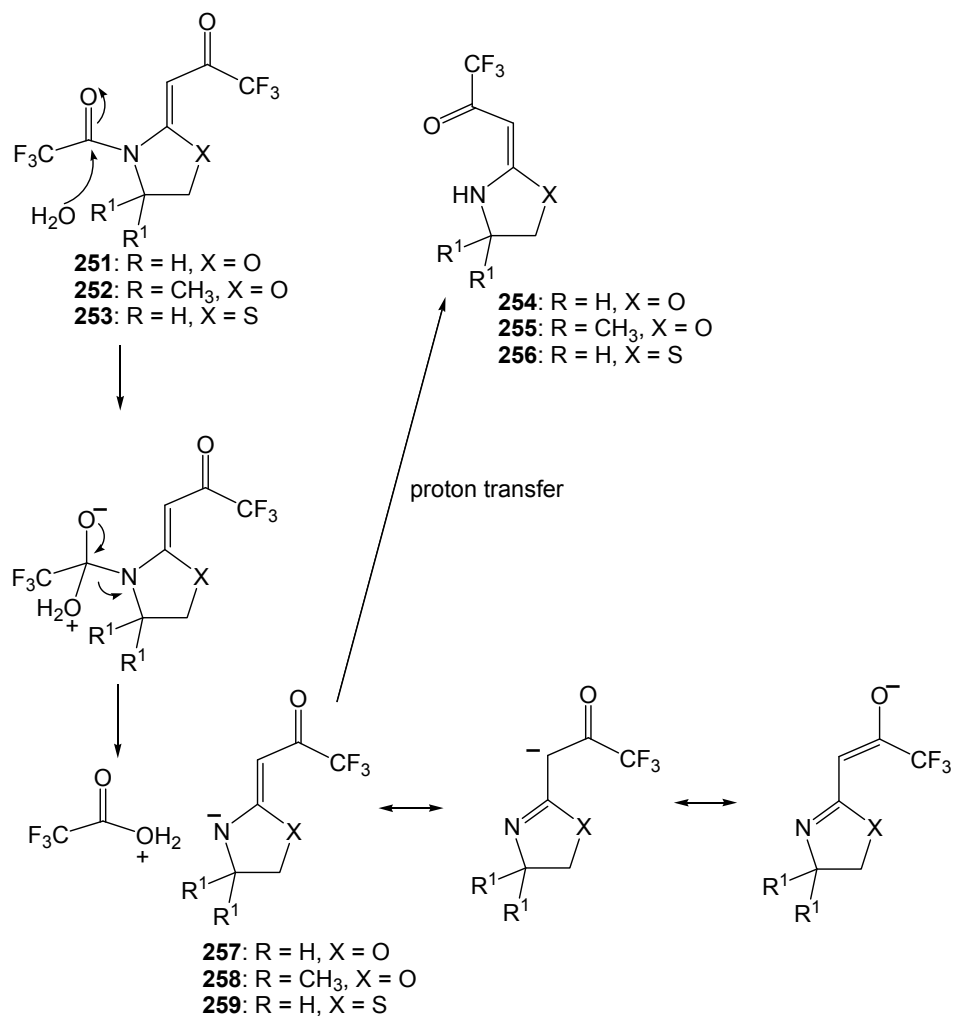
Results and discussion

Trifluoroacetylations of 2-methyl-2-oxazoline, 2,4,4-trimethyl-2-oxazoline and 2-methyl-2-thiazoline didn't give the *N,C*-bistrifluoroacetylated cyclic ketene-*N,O*-acetals **251-253** (Equations 5.3-5, respectively). Instead, only the mono *C*-acylation products **254-256** were obtained.





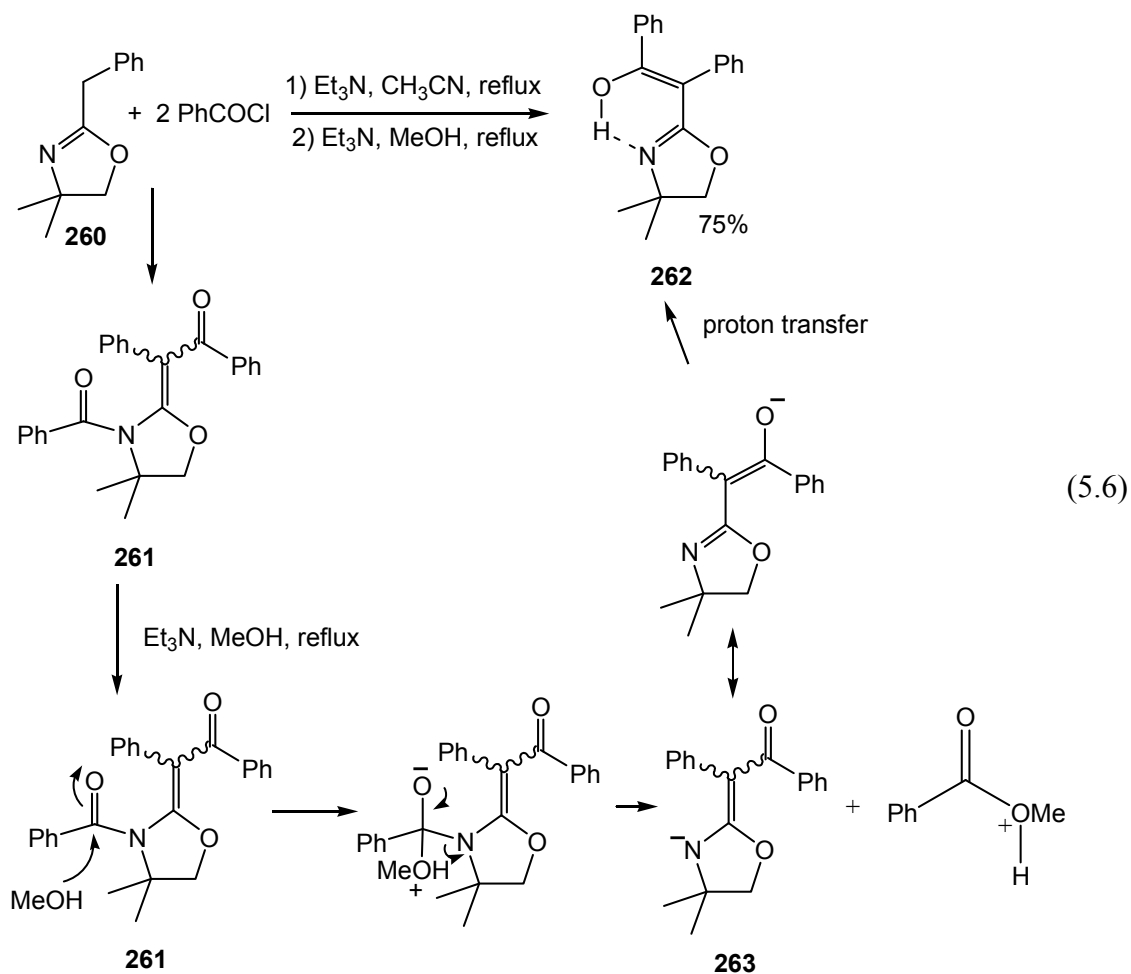
These reactions presumably involve *N,C*-bistrifluoroacetylated products **251-253** as the intermediates (Scheme 5.1). However, these strongly electrophilic trifluoroacetic moieties on the nitrogen of intermediates **251-253** would be highly susceptible to nucleophilic attack. The trifluoroacetyl function on the β -carbon helps to stabilize the incipient conjugated anions (**257-259** in Scheme 5.1) formed upon loss of the *N*-trifluoroacetyl function. The nucleophile responsible for this *N*-deacylation could be the trifluoroacetate anion, but more likely this *N*-deacylation occurred at the aqueous workup to give ambident anions **257-259**. The speculative *N,C*-bistrifluoroacetylated products **251-253** can not survive even the typical TLC conditions. No attempts were made to isolate or observe **251-253** using anhydrous workups or to take NMR spectra of reaction product solutions.



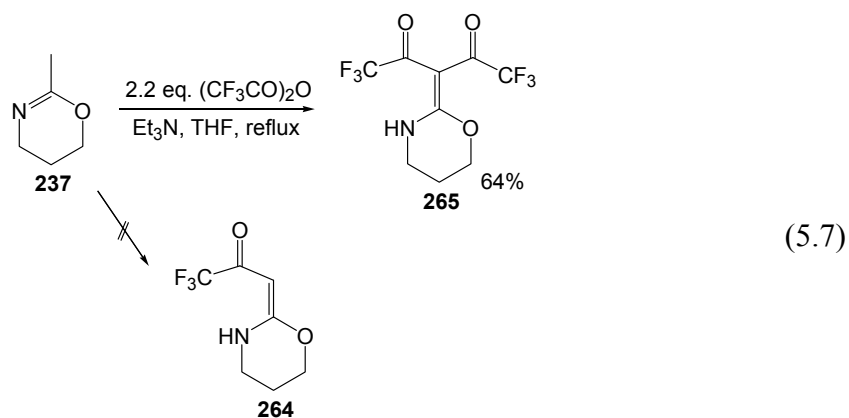
Scheme 5.1 A possible mechanism for *N*-deacylation of **251-253** by water

One literature example suggests the above interpretation is reasonable.⁵⁰

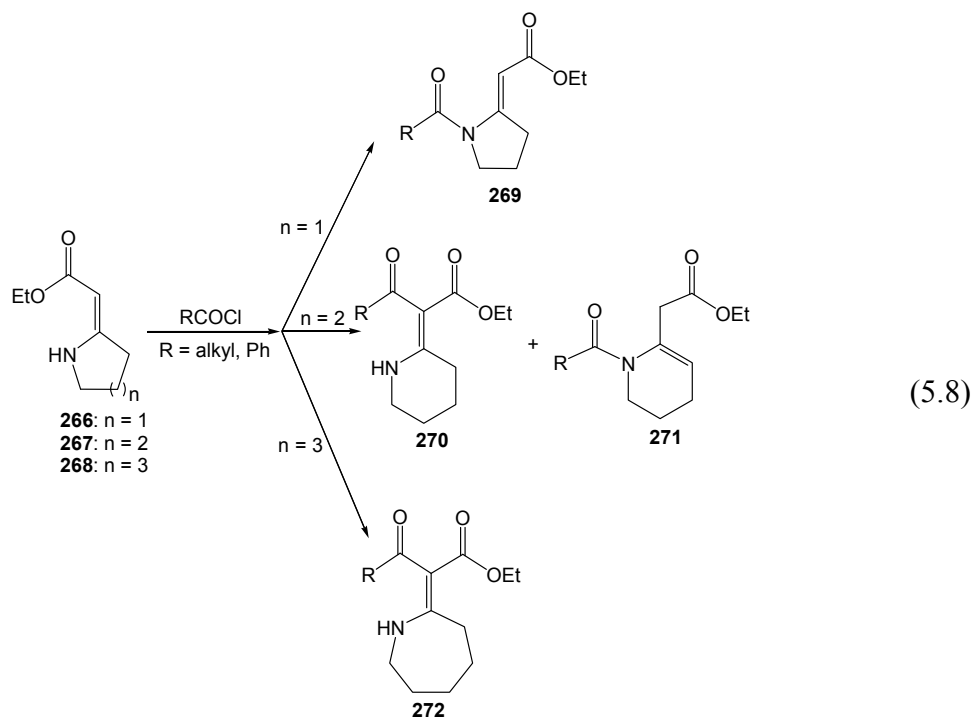
Benzoylation of **260** gave *N,C*-bisbenzoylated cyclic ketene-*N,O*-acetal **261**, which was *N*-deacylated by methanol to give **262** in 75 % yield (Equation 5.6). The phenyl and the keto functions at the β -carbon help to stabilize anion **263** formed during *N*-deacylation.



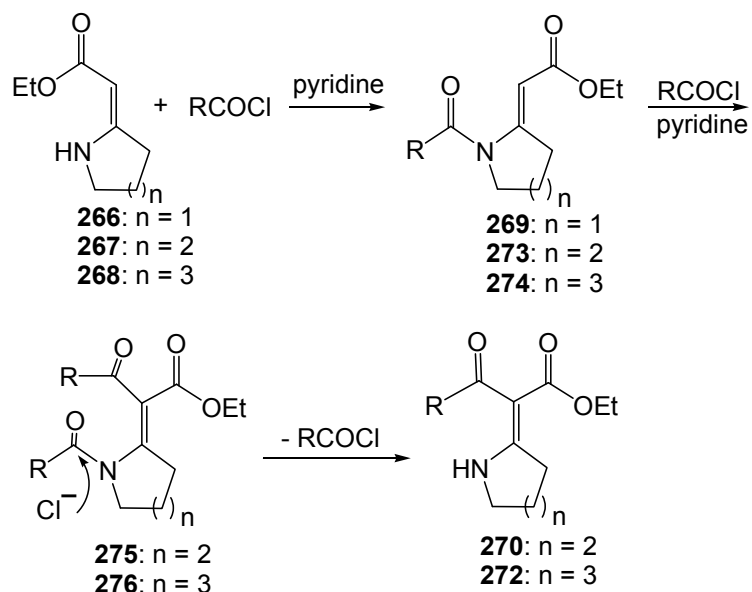
This trifluoroacetylation was extended to 2-methyl-2-oxazine (**237**). Surprisingly, the β -monotrifluoroacetylated cyclic ketene-*N,O*-acetal **264**, was not isolated. Instead, β,β -bistrifluoroacetylated cyclic ketene-*N,O*-acetal **265** was obtained (Equation 5.7).



There is a literature analogy in cyclic enaminoester acylations (Equation 5.8)⁵² when we assume that the different trifluoroacetylation paths displayed by 2-methyl-2-oxazoline and 2-methyl-2-thiazoline versus 2-methyl-2-oxazine all go through *N,C*-bistrifluoroacetylation stage. Five-membered enaminoester **266** underwent only *N*-acylation, while six- and seven-membered enaminoesters **267** and **268** underwent *C*-acylation under the same conditions.



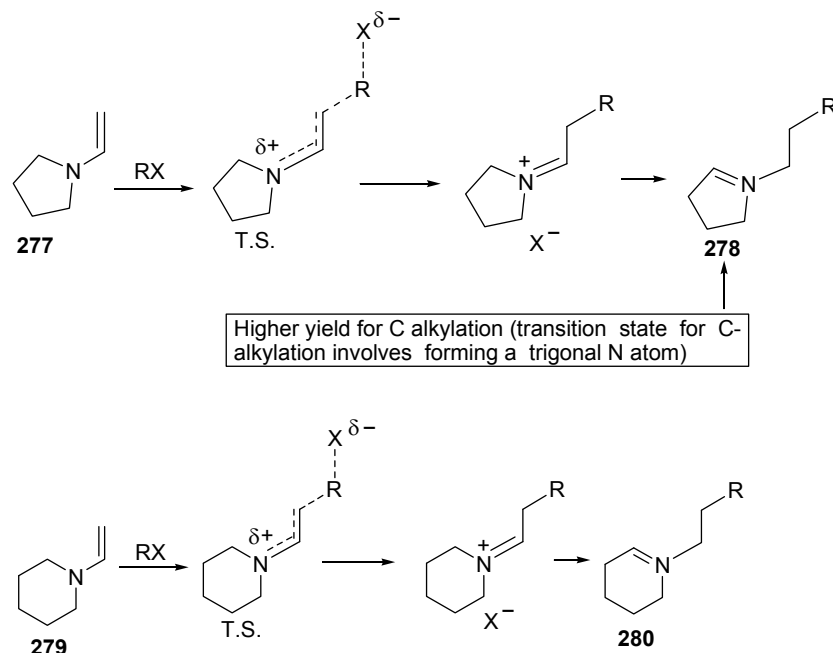
N-acylation was proposed⁵² (Scheme 5.2) to have occurred first for 5, 6 and 7-membered enaminoesters to give **269**, **273** and **274**. The 5-membered *N*-acylated enaminoester **269** could not be acylated further. In contrast, **273** and **274** reacted with two equivalents of RCOCl to give β -acylation products **275** and **276**, followed by *N*-deacylation by chloride anion to give β,β -disubstituted adducts **270** and **272**.



Scheme 5.2 Six and seven-membered enaminoesters undergo *N*-acylation, β -acylation and *N*-deacylation by chloride anion to give β,β -disubstituted adducts **270** and **272**.

The underlying reason for this difference in behavior was not accounted for in that paper. H. C. Brown⁵³ pointed out the reactivity difference between a carbon-carbon double bond *exo* to a 6-membered ring and a carbon-carbon double bond *exo* to a 5-membered ring, i.e., reactions which involved the loss of an exocyclic double bond will be favored in the 6-membered ring as compared to the corresponding 5-membered ring. In other words, double bonds which are exocyclic to a 5-membered ring are less reactive and more stable (relative to the saturated derivatives) than related double bonds which are exocyclic to a 6-membered ring. Stork⁴⁹ (Scheme 5.3) used this argument to explain why pyrrolidine enamine **277** gave C-alkylation product **278** in a higher yield than the piperidine enamine **279** gave **280**. Since the transition state for C-alkylation (but not for *N*-alkylation) involves forming a trigonal atom in the amine portion of the molecule, one

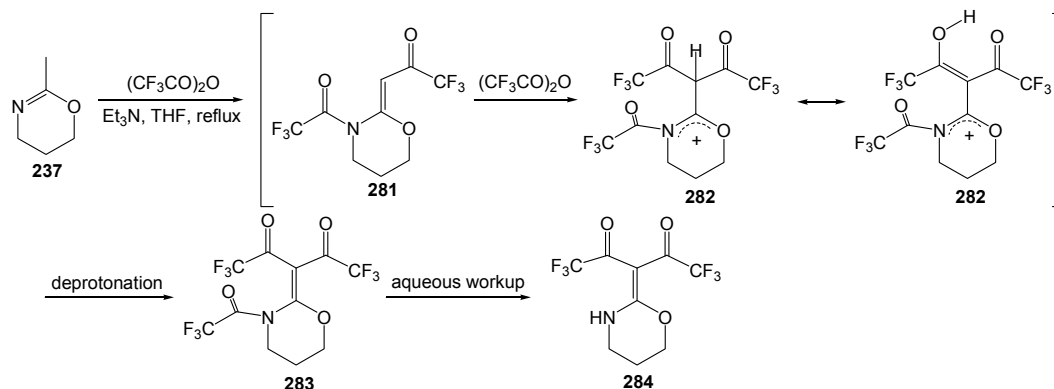
observes the most favorable ratio of C to N alkylation to be obtained with the pyrrolidine enamines.



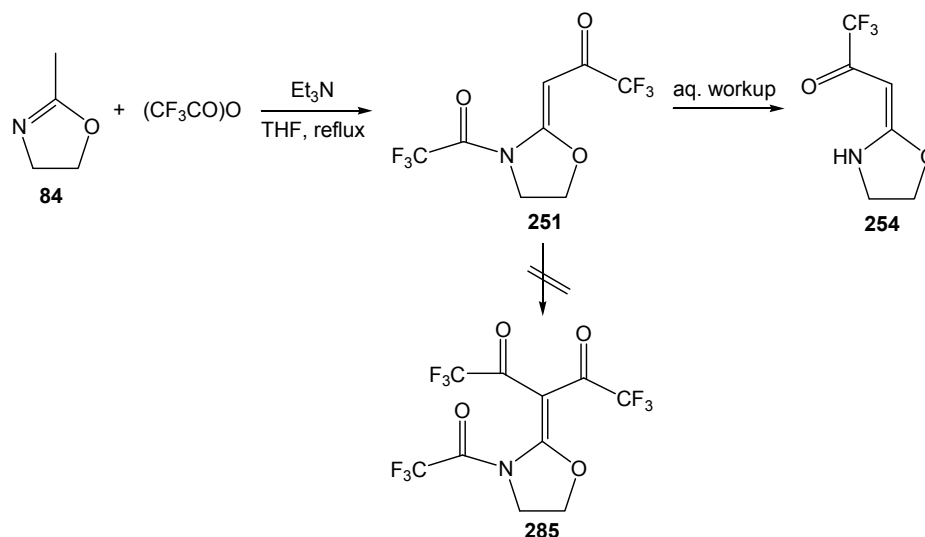
Scheme 5.3 C-alkylation of the pyrrolidine enamine **277** involves formation of a trigonal nitrogen on a five-membered ring, which is easier than its six-membered analog

This argument is applied to the reactions reported here. The six-membered ring *N,C*-bistrifluoroacetylation intermediate **281** is proposed to undergo a third acylation at its β -carbon, forming intermediate **282** (Scheme 5.4). The exocyclic carbon-carbon double bond is lost and a stable oxazolinium cation is formed, where the charge is delocalized over O, N and C-2. Subsequent deprotonation of **282**, or its enol form, gives **283**. Highly reactive **283** is easily *N*-detrifluoroacetylated by water during workup to form β,β -ditrifluoroacetylation product **284**. By contrast, the exocyclic C=C bond of the five membered *N,C*-bistrifluoroacetylation product **251** is more stable (relative to **281**)

and resists a third acylation to give **285**. Compound **251** is easily deacylated by water during workup to give monotrifluoroacetylated **254** (Scheme 5.5).



Scheme 5.4 Six-membered *N,C*-bistrifluoroacetylated cyclic ketene-*N,O*-acetal **281** undergoes a third acylation at its β -carbon



Scheme 5.5 Five-membered *N,C*-bistrifluoroacetylated cyclic ketene-*N,O*-acetal **251** resists a third acylation at its β -carbon

Cyclic ketene-*N,O*-acetals **254-256** are ambident nucleophiles as are their corresponding anions **257-259** (Figure 5.1). The crystal structure of the five-membered ring system **255** (Figure 5.2) showed that the distance between hydrogen on the ring

nitrogen and the β -carbonyl oxygen is 2.298 Å, suggesting that the intramolecular hydrogen bond, if present, is very weak. This is in contrast with the crystal structure of the six-membered ring analog **265** (Figure 5.3), which has an intramolecular hydrogen bond of 1.999 Å. H-bond is occurring in **265**. This difference also accounts for the NH peak shape difference in ^1H NMR. The NH peak of **255** is broad due to rapid intermolecular exchange. In contrast, the NH peak is sharp for **265**. The weak intramolecular hydrogen bond in **255** means the NH proton has more freedom and likely engages in intermolecular hydrogen bonding, leading to peak broadening. In contrast, the strong intramolecular hydrogen bond in **265** holds the NH proton in place, leading to a sharp peak.

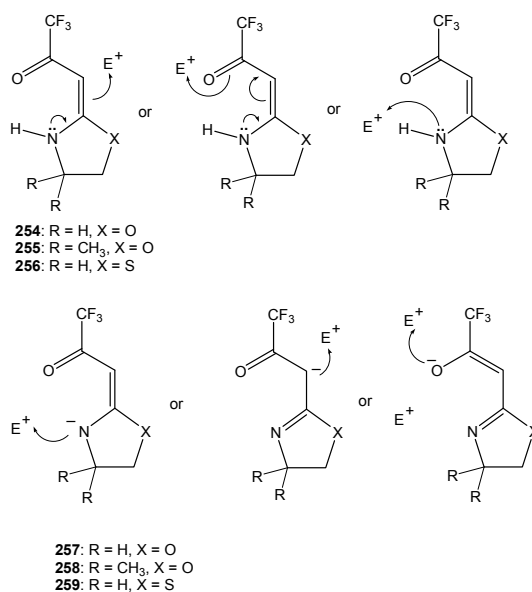


Figure 5.1 Cyclic ketene-*N,O*-acetals **254-256** and their corresponding anions **257-259** are ambident nucleophiles

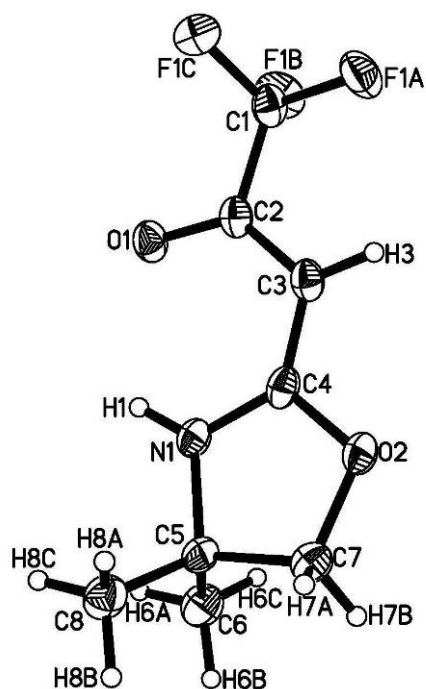


Figure 5.2 The crystal structure of 3-(4,4-dimethyloxazolidin-2-ylidene)-1,1,1-trifluoropropan-2-one (**255**). CCDC: 796901

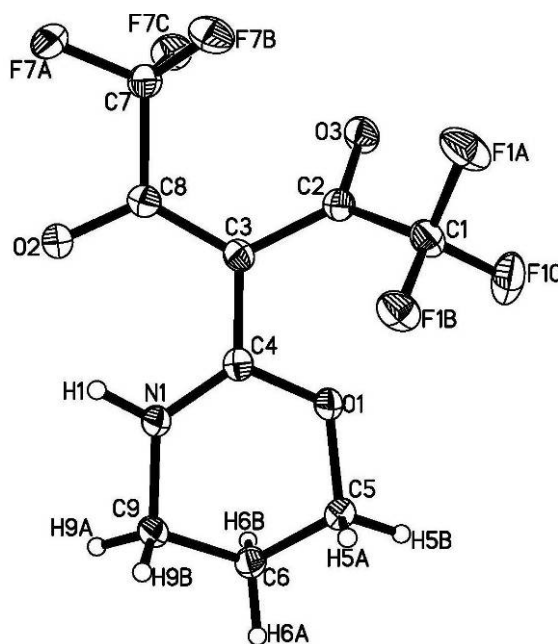


Figure 5.3 The crystal structure of 1,1,1,5,5,5-hexafluoro-3-[1,3]oxazinan-2-ylidene-pentane-2,4-dione (**265**). CCDC: 796902

1-Phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-ethanone (**90**) is less nucleophilic at its β -carbon than its precursor **27**, due to the presence of the electron withdrawing β -benzoyl group and due to the benzoyl group's larger size versus a hydrogen (Figure 5.4). However, **90** might still react with a stronger electrophile, like trifluoroacetic anhydride. Therefore, to shed more light on cyclic ketene-*N,O*-acetal reactivity, this reaction was tried. If trifluoroacetylation of **90** was successful, 4,4,4-trifluoro-1-phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-butane-1,3-dione (**286**) should result (Equation 5.9). This compound, a β,β -disubstituted push-pull cyclic ketene-*N,O*-acetal, is of interest in terms of its structure, the length of the exocyclic bond to the β -carbon and the rotational barrier about this bond.^{46b}

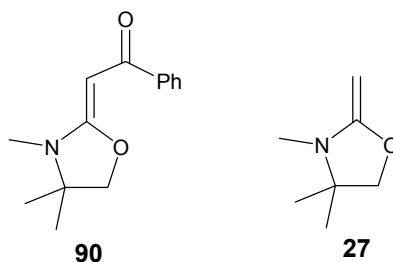
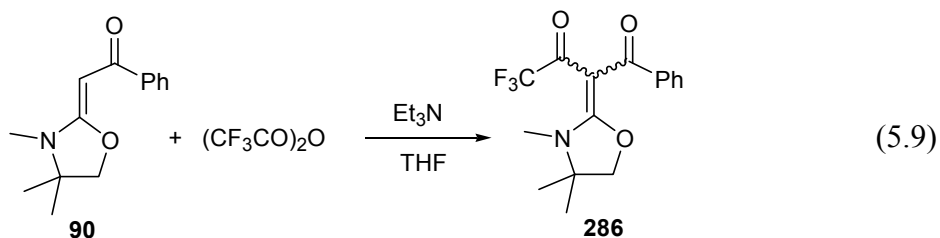
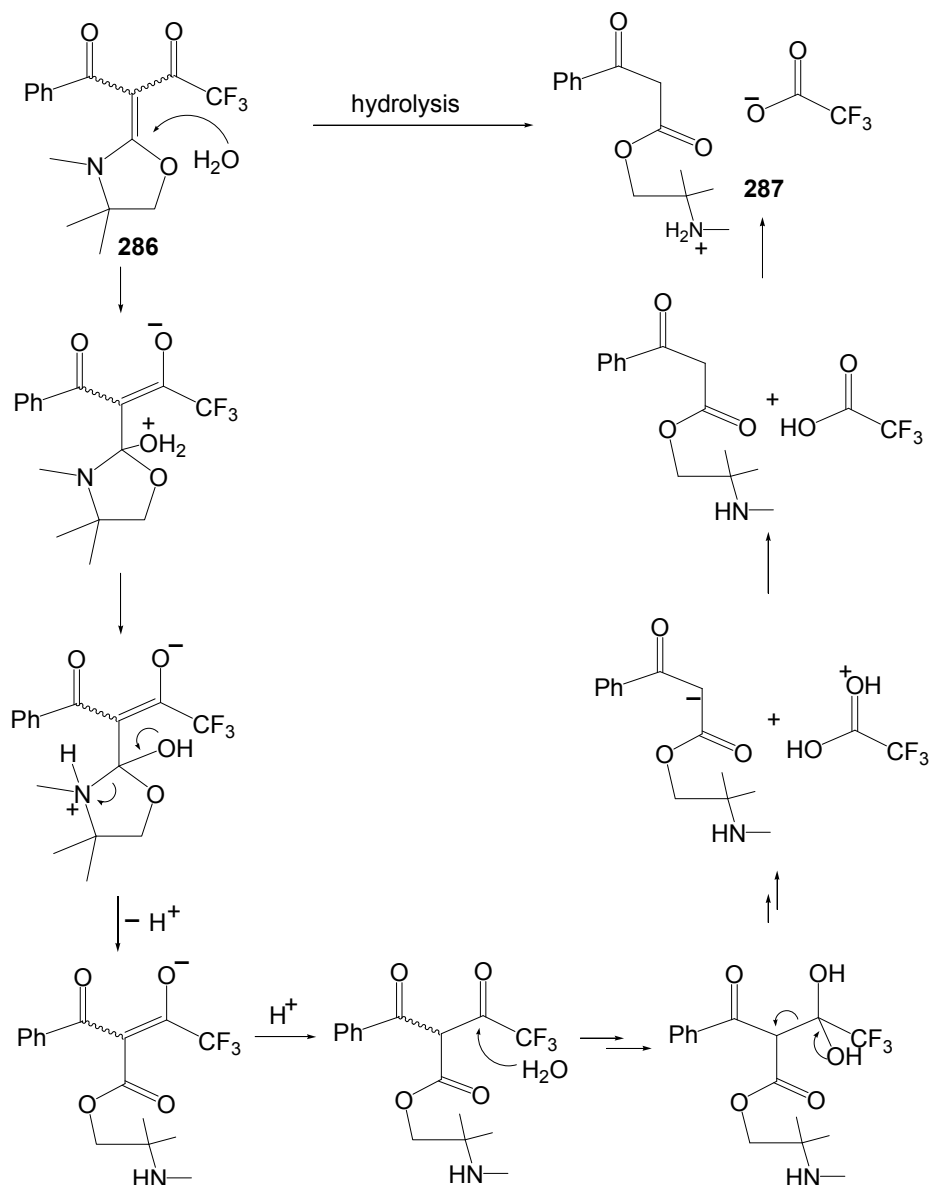


Figure 5.4 β -Keto cyclic ketene-*N,O*-acetal **90** is less nucleophilic at its β -carbon than its precursor **27**



1-Phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-ethanone (**90**) (1 eq.), triethylamine (1.23 eq.) and trifluoroacetic anhydride (1.18 eq.) were refluxed in CH_3CN for 4.5 h. Workup and column chromatography successfully gave 4,4,4-trifluoro-1-

phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-butane-1,3-dione (**286**) in 29.4 % yield. The structure of **286** was confirmed by ^1H NMR and ^{13}C NMR. However, whether the (*Z*) or (*E*) geometric isomer of **286** was obtained is not clear, despite the effort to solve this problem by NOESY. The exocyclic carbon-carbon double bond of β,β -disubstituted push-pull cyclic ketene-*N,O*-acetals usually displays significant bond elongation,^{46b} indicating a reduced bond order. This lowers their rotational barriers. Therefore, attempts were made to grow single crystals of **286** from acetone/hexanes and DCM/hexanes in order to use XRD to resolve the geometrical isomer's (*Z*) or (*E*) identity in the solid state. Unfortunately, these attempts were not successful. Instead, the hydration product, [1,1-dimethyl-2-(3-oxo-3-phenylpropionyloxy)-ethyl]-methyl-ammonium trifluoroacetate (**287**), a salt (Scheme 5.6), was isolated and its structure was determined by XRD. This conversion from **286** to **287** occurred either during the storage of **286** (prior to recrystallization) or while conducting recrystallization attempts. A rationale for this is proposed in Scheme 5.6. Clearly, **286** is easily attacked by water because of its highly polarized zwitterionic-like structure, which we predict has a significant out-of-plane tilt angle between the five-membered ring and the plane defined by the carbonyl carbons and β -carbon.



Scheme 5.6 Hydration of β,β -disubstituted push-pull cyclic ketene-*N,O*-acetal **286**

In summary, a new reaction path has been found in trifluoroacetylation of 2-methyl-2-oxazolines, 2-methyl-2-thiazoline and 2-methyl-2-oxazine. A ring size effect on β -bis trifluoroacetylation was also discovered. The β,β -bistrifluoroacetylation of 2-methyl-2-oxazine not only generated a new push-pull structure but also shed light on the

subtle reactivity differences found among cyclic ketene-*N,O*-acetals of different ring sizes.

Experimental

Descriptions on materials and instruments involved in this chapter can be found in experimental part of Chapter 2.

Preparation of (*E*)-1,1,1-trifluoro-3-oxazolidin-2-ylidene-propan-2-one (254)

2-Methyl-2-oxazoline (**84**) (2.32 g, 26.7 mmol, 1 eq.) was placed in a 100 mL flask, followed by dried THF (67 mL) and triethylamine (6.35 g, 62.4 mmol, 2.34 eq.). At ice bath temperature, (CF₃CO)₂O (13.5 g, 63.7 mmol, 2.38 eq.) was added dropwise over 19 min. The resulting suspension was refluxed for 5 h under nitrogen. Rotary evaporation was used to remove the solvent. Dichloromethane (30 mL) and saturated NaHCO₃ (38 mL) were added to the residue and the mixture was stirred for 10 min. The organic layer was washed further with water (2 x 40 mL). The organic layer was dried over anhydrous Na₂SO₄. After concentrating by rotary evaporation, the crude product was purified by flash column chromatography over silica gel, using mixed ethyl acetate/hexanes (2: 1 volume ratio) as the eluting solvent. White solid (1.49 g, 8.23 mmol) were obtained, yield 30.8 %. ¹H NMR (300 MHz, CDCl₃): δ 9.77 (s, br, NH, 1H), 5.29 (s, =CH-CO-, 1H), 4.61 (s, -O-CH₂-, J = 8.7 Hz, 2H), 3.90 (>N-CH₂-, J = 8.7 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 175.2 (COCF₃, quartet, J = 33.1 Hz), 171.7 (N,O>C=), 117.8 (CF₃, quartet, J = 288.0 Hz), 72.6 (=C(COCF₃), 68.2 (-OCH₂-), 43.0 (>N-CH₂-). IR (neat, cm⁻¹): 3251, 1637, 1568, 1341, 1292, 1222, 1112, 1042, 968, 758, 692. mp 120-121 °C.

Preparation of (E)-3-(4,4-dimethyloxazolidin-2-ylidene)-1,1,1-trifluoropropan-2-one (255)

The title compound **255** was prepared using 2,4,4-trimethyl-2-oxazoline (**100**) (1.50 g, 13.1 mmol, 1 eq.), trifluoroacetic anhydride (6.52 g, 30.7 mmol, 2.34 eq.) and triethylamine (3.11 g, 30.6 mmol, 2.33 eq.) by the procedure for preparation of **254**. A white solid (1.34 g) was obtained, yield 48.8 %. ^1H NMR (300 MHz, CDCl_3 , Figure 5.5): δ 9.86 (s, br, NH, 1H), 5.16 (s, $=\text{CH}-\text{CO}-$, 1H), 4.19 (s, $-\text{O}-\text{CH}_2-$, 2H), 1.42 ($>\text{N}-\text{C}(\text{CH}_3)_2$, 6H). ^{13}C NMR (75 MHz, CDCl_3 , Figure 5.6): δ 175.1 ($\text{C}=\text{O}$, quartet, $J = 32.6$ Hz), 170.2 ($\text{N}, \text{O}=\text{C}=\text{CH}-$), 117.9 (CF_3 , quartet, $J = 288.6$ Hz), 79.7 ($=\text{C}(\text{C}=\text{O})$), 72.5 ($-\text{OCH}_2-$), 59.6 ($\text{N}-\text{C}(\text{CH}_3)_2$), 26.5 ($>\text{N}-\text{C}(\text{CH}_3)_2$). IR (neat, cm^{-1}): 3266, 1640, 1566, 1321, 1162, 1130, 1006, 695. mp 140-141 $^\circ\text{C}$.

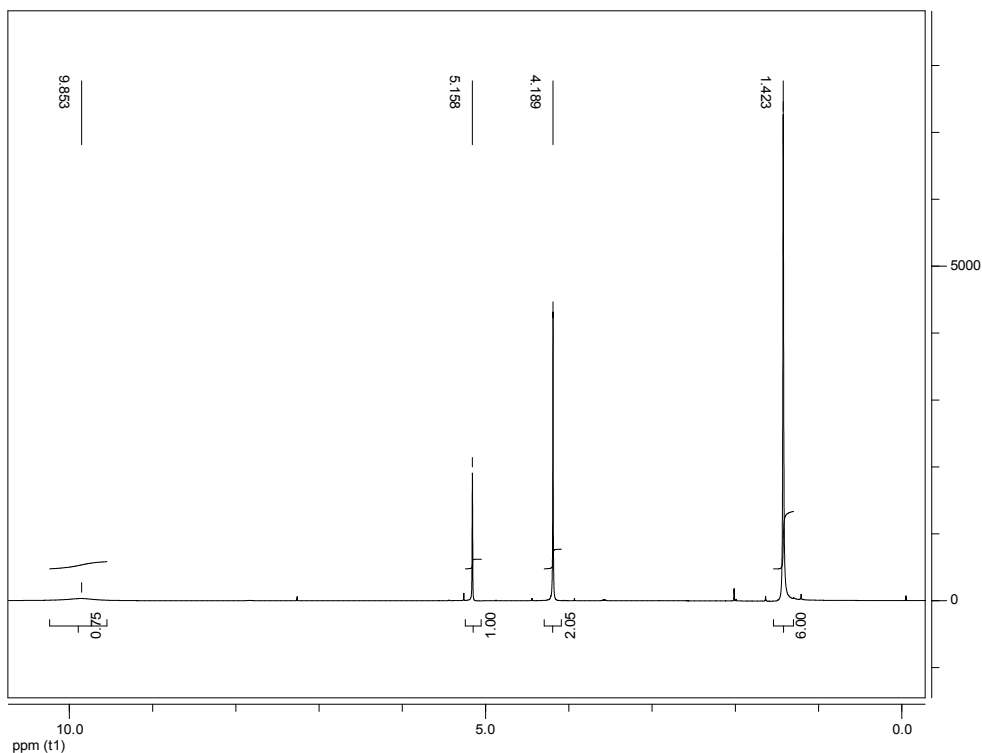


Figure 5.5 ^1H NMR of 3-(4,4-dimethyloxazolidin-2-ylidene)-1,1,1-trifluoropropan-2-one (**255**)

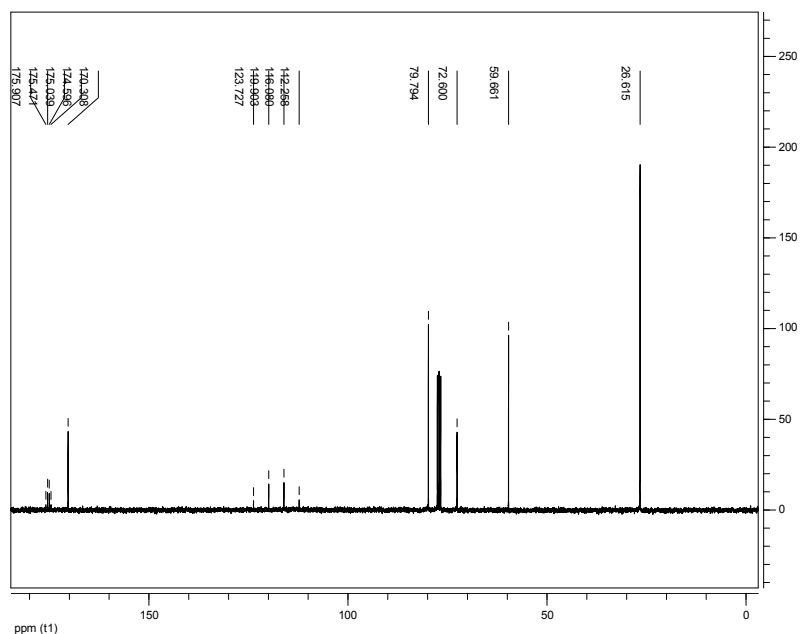


Figure 5.6 ^{13}C NMR of 3-(4,4-dimethyloxazolidin-2-ylidene)-1,1,1-trifluoropropan-2-one (**255**)

Preparation of (*E*)-1,1,1-trifluoro-3-thiazolidin-2-ylidene-propan-2-one (**256**)

The title compound **256** was prepared using 2-methyl-2-thiazoline (2.62 g, 25.6 mmol, 1 eq.), trifluoroacetic anhydride (13.02 g, 61.3 mmol, 2.39 eq.) and triethylamine (6.11 g, 60.1 mmol, 2.34 eq.) by the general procedure described for the trifluoroacetylation of 2-methyl-2-oxazoline (**84**), except that recrystallization from ethyl acetate/hexanes was employed for purification. White needle like crystals (2.21 g) were obtained from two successive recrystallizations, yield 43.8 %. ^1H NMR (300 MHz, CDCl_3): δ 10.51 (s, br, NH, 1H), 5.60 (s, =CH-CO-, 1H), 4.04 (t, -O-CH₂-, J = 7.8 Hz, 2H), 3.36 (t, >N-CH₂-, 7.8 Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 174.6 (N,S>C=), 173.8 (C=O-CF₃, quartet, J = 32.9 Hz), 117.6 (CF₃, quartet, J = 288.4 Hz), 83.6 (=C(CO-CF₃), 50.2 (>N-CH₂-), 29.2 (-SCH₂-). IR (neat, cm^{-1}): 3217, 1603, 1560, 1500, 1314, 1105, 1045, 935, 886, 766, 722, 682, 576. mp 123-125 °C.

Preparation of 1,1,1,5,5,5-hexafluoro-3-[1,3]oxazinan-2-ylidene-pentane-2,4-dione (**265**)

The title compound **265** was prepared using 2-methyl-2-oxazine (**237**) (0.40 g, 4.04 mmol, 1 eq.), trifluoroacetic anhydride (1.91 g, 9.00 mmol, 2.23 eq.) and triethylamine (0.94 g, 9.24 mmol, 2.29 eq.) by the procedure for preparation of **254**. Chromatography over silica gel, using mixed acetone/hexanes (1:2 volume ratio) as the eluting solvent. A white solid (0.75 g) was obtained, yield 63.8 %. ^1H NMR (300 MHz, CDCl_3 , Figure 5.7): δ 11.12 (s, br, NH, 1H), 4.46 (t, -O-CH₂-, J = 5.4 Hz, 2H), 3.59 (t, >N-CH₂-, J = 6.0 Hz, 2H), 2.21 (m, -CH₂-CH₂-CH₂-, 2H). ^{13}C NMR (75 MHz, CDCl_3 , Figure 5.8): δ 167.4 (N,O>C=), 116.5 (CF₃, quartet, J = 289.4 Hz), 92.4 (=C(COCF₃)), 67.1 (-OCH₂-), 37.6 (>N-CH₂-), 19.8 (-CH₂-CH₂-CH₂-). The COCF₃ peak is missing. Literature search for compounds with similar structure =C(COCF₃)₂ only found their ^1H NMRs. IR (neat, cm^{-1}): 3197, 1699, 1632, 1602, 1503, 1380, 1267, 1192, 1126, 1053, 934, 870, 836, 727, 715. mp 94-95 °C.

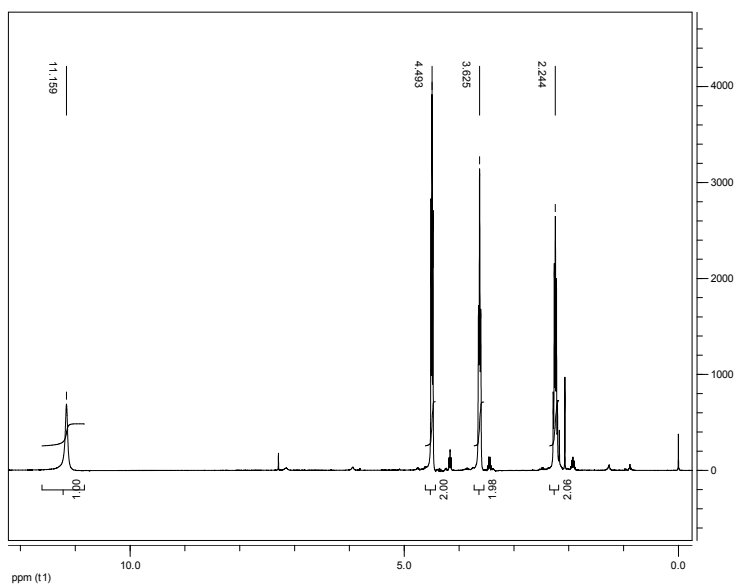


Figure 5.7 ^1H NMR of 1,1,1,5,5,5-hexafluoro-3-[1,3]oxazinan-2-ylidene-pentane-2,4-dione (**265**)

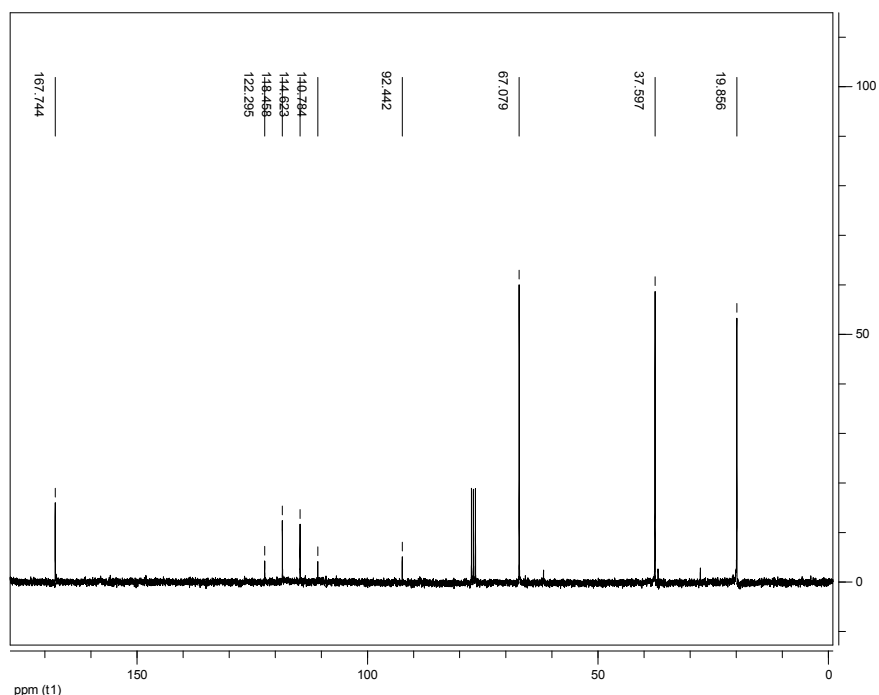


Figure 5.8 ^1H NMR of 1,1,1,5,5,5-hexafluoro-3-[1,3]oxazinan-2-ylidene-pentane-2,4-dione (**265**)

Preparation of 1,1,1,5,5,5-hexafluoro-3-[1,3]oxazinan-2-ylidene-pentane-2,4-dione (**265**), using DIPEA as the base

The title compound **265** was prepared using 2-methyl-2-oxazine (**237**) (0.38 g, 3.84 mmol, 1 eq.), trifluoroacetic anhydride (1.82 g, 8.58 mmol, 2.23 eq.) and DIPEA (1.16 g, 8.93 mmol, 2.33 eq.) by the procedure for preparation of **254**. After the reaction, 4.65 g of the reaction mixture was taken for ^1H NMR. However, the NMR thus obtained for the crude reaction mixture was too messy and no useful information can be take from the NMR (for example, there was a triplet like peak at around 5ppm position. We were not sure whether this peak is the β -vinyl proton of the *N,C*-bistrifluoroacetylation product or not). Chromatography over silica gel, using mixed acetone/hexanes (1:2 volume ratio) as the eluting solvent. Compound **265** (white solid, 0.70 g, mp 94-95 °C) was obtained in 62.7 % yield.

Preparation of 4,4,4-trifluoro-1-phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-butane-1,3-dione (**286**)

1-Phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-ethanone (**90**) (0.74 g, 3.2 mmol, 1 eq.) was put into a flask, followed by dried CH₃CN (22 mL) and 0.51 g dried Et₃N (3.93 mmol, 1.23 eq.). Then trifluoroacetic anhydride (0.80 g, 3.78 mmol, 1.18 eq.) was added dropwise over 9 min to the mixture at ice bath temperature, under nitrogen. The mixture was stirred for 4.5 h at reflux. After the mixture was cooled to room temperature, rotary evaporation was used to remove the solvent. Then DCM (15 mL) and deionized water (30 mL) were added and the mixture was stirred for 10 min. The organic layer was washed further with brine (20 mL) once and dried over anhydrous Na₂SO₄. After concentration with rotary evaporation, the crude product was purified by flash column chromatography over SiO₂ gel, using ethyl acetate/hexanes (2.5:1 volume ratio) as eluting solvent. 4,4,4-Trifluoro-1-phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-butane-1,3-dione (**286**) was obtained (yellow solid, 0.307 g, yield 29.4 %). ¹H NMR (300 MHz, CDCl₃): δ 1.39 (s, >N-C(CH₃)₂-, 6H), 2.84 (s, >N-CH₃, 3H), 4.10 (s, -OCH₂-, 2H), 7.33 -7.70 (aromatic, 5H). ¹³C NMR (75 MHz, CDCl₃): δ 191.4 (N,O>C=), 175.9 (-COPh or -COCF₃), 172.6 (-COPh or -COCF₃), 140.3 (aromatic), 131.3 (aromatic), 128.0 (aromatic), 127.9 (aromatic), 117.3 (CF₃, quartet, J = 291 Hz), 91.5 (=C(COPh)COCF₃), 77.9 (-OCH₂-), 64.1 (N-C(CH₃)₂), 30.0 (>N-CH₃), 23.2 (>N-C(CH₃)₂-). mp 116-118 °C. IR (neat, cm⁻¹): 2967, 2360, 1602, 1564, 1420, 1177, 1127, 962, 854, 790, 697, 638.

Compound **286** was stored sixteen months on benchtop and recrystallized from DCM. Single crystals thus obtained turned out to be [1,1-dimethyl-2-(3-oxo-3-

phenylpropionyloxy)-ethyl]-methyl-ammonium trifluoroacetate (**287**), which is the hydration product of **286**. The crystal structure of **287** is shown in Figure 5.9.

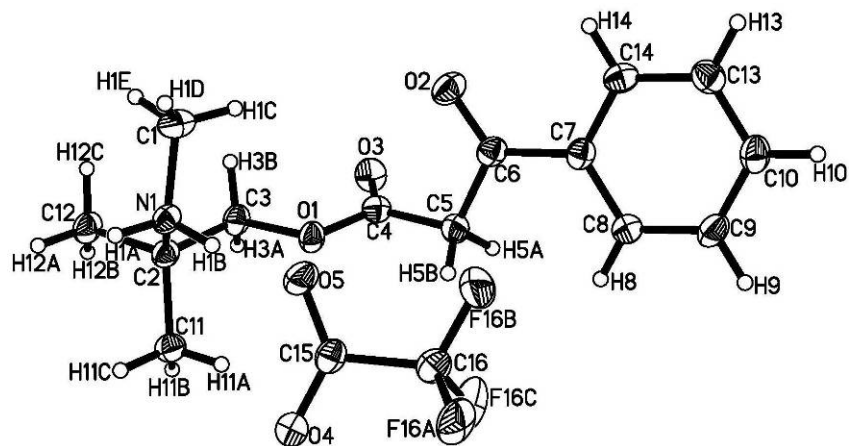


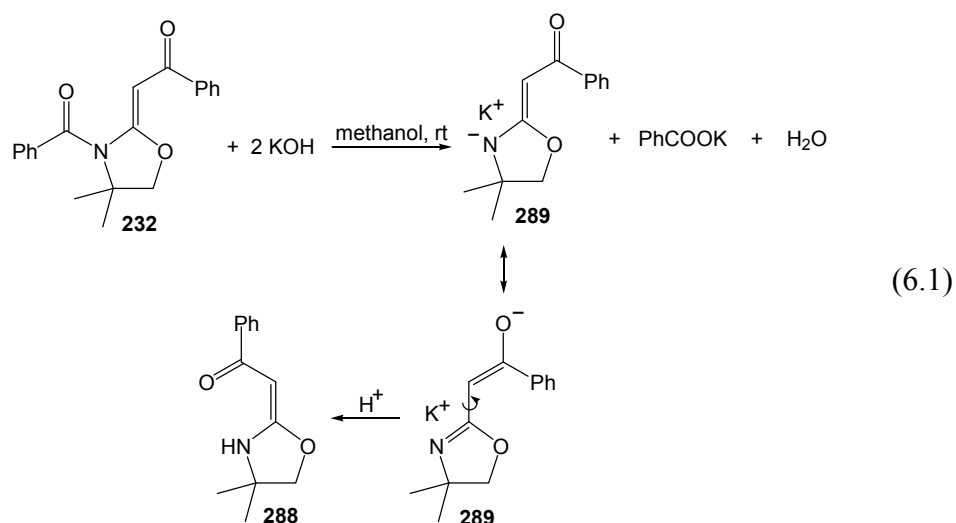
Figure 5.9 The crystal structure of [1,1-dimethyl-2-(3-oxo-3-phenylpropionyloxy)-ethyl]-methyl-ammonium trifluoroacetate (**287**)

CHAPTER VI

REACTIONS OF 2-OXAZOLIDIN-2-YLIDENE-1-PHENYLETHANONE AND ITS
ANION WITH ELECTROPHILES

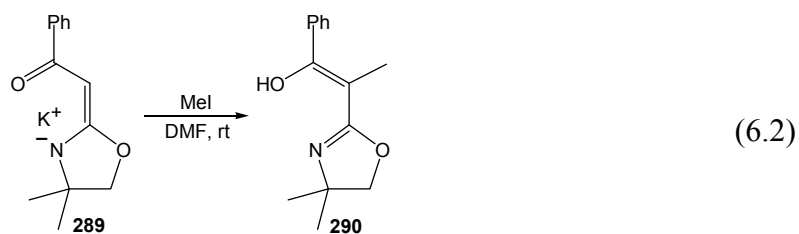
Introduction

2-(4,4-Dimethyloxazolidin-2-ylidene)-1-phenylethanone (**288**) was first made by Tohda⁵⁰ from the *N*-debenzoylation of cyclic ketene-*N,O*-acetal **232** (Equation 6.1).

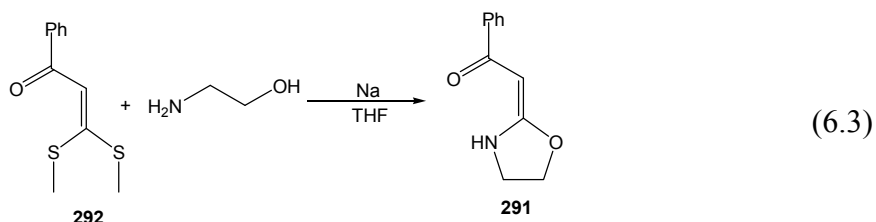


The *N*-benzoyl function of **232** is easily deacylated by hydroxide due to the presence of the electron withdrawing β -benzoyl function, which helps to stabilize the resulting anion **289**. This anion is an ambident nucleophile; its ring nitrogen, β -carbon and the oxygen of the β -carbonyl function are all nucleophilic. Reaction of this anion with methyl iodide led to β -carbon methylation to form **290**⁵⁰ (Equation 6.2). No other reactions of anion **289** with other electrophiles have been explored. As a continuation of

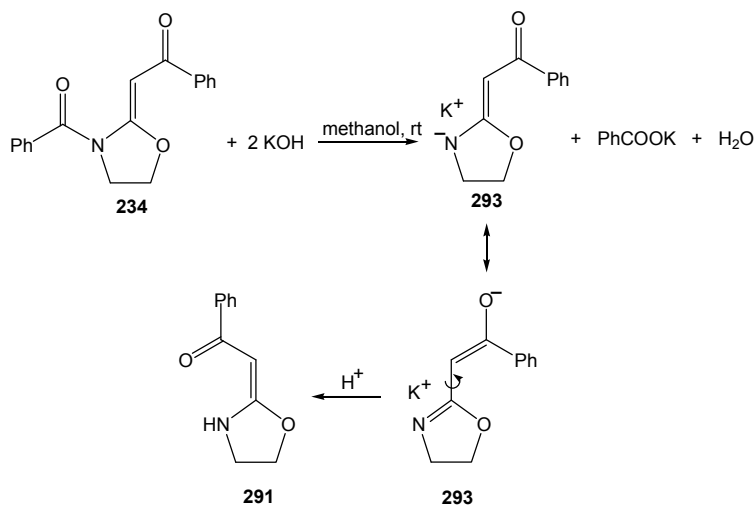
the exploration of cyclic ketene-*N,O*-acetal-based chemistry, the reaction of this type of anion with the electrophiles benzoyl chloride and phenyl chloroformate were studied.



2-Oxazolidin-2-ylidene-1-phenylethanone (**291**), an analog of 2-(4,4-dimethyloxazolidin-2-ylidene)-1-phenylethanone (**288**), was previously made from the reaction between ketene dithioacetal **292** and 2-aminoethanol⁵⁴ (Equation 6.3).



In analogy to Equation 6.1, another route to **291** could be *N*-debenzoylation of cyclic ketene-*N,O*-acetal **234**, via intermediate anion **293** (Scheme 6.1).



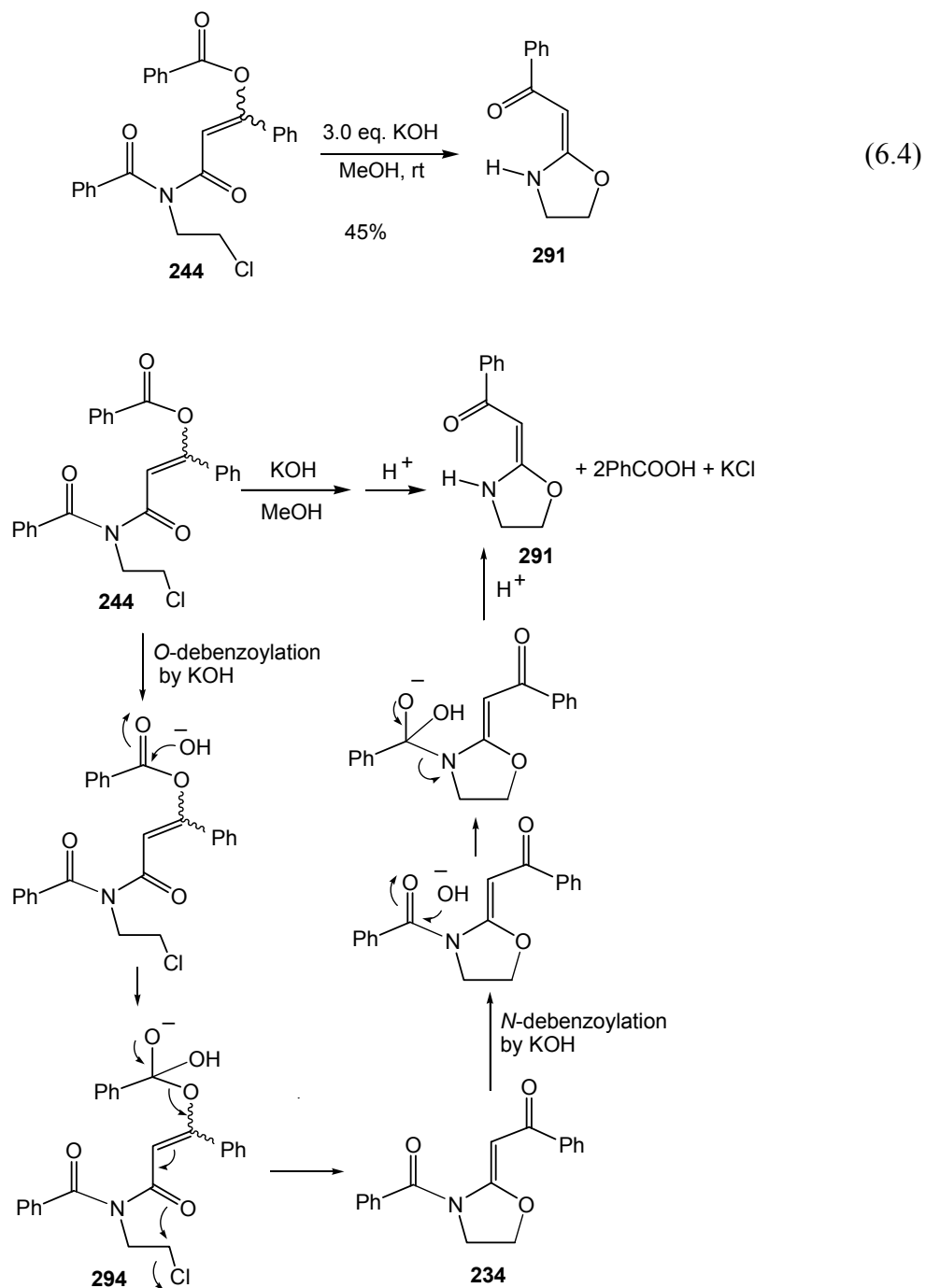
Scheme 6.1 A possible route to **291** from *N*-debenzoylation of **234**

However, **234** could not be prepared this way because the *C,N*-dibenzoylation of 2-methyl-2-oxazoline (**84**) could not be achieved. Instead, attempts at dibenzoylation only gave ring-opened compound **244** (see chapter 4 and Equation 6.4).

It occurred to us that cyclic ketene-*N,O*-acetal **291** might be made from **244** via a double O and N debenzoylation followed by intramolecular oxygen attack on the carbon bearing chlorine. If this route works, it would provide another way to make **291** besides that shown in Equation 6.3 from ketene dithioacetal and 2-aminoethanol. Furthermore, since a stock of **244** was already in hand, this would serve as a simple one step preparation of **291**.

Results and discussion

3-[Benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (**244**), upon treatment with KOH/MeOH, gave 2-oxazolidin-2-ylidene-1-phenylethanone (**291**), in 45 % yield (Equation 6.4). It seems likely (see Scheme 6.2) that *O*-debenzoylation by hydroxide sets off a subsequent intramolecular S_N2 attack by a carbonyl oxygen of **243** on the methylene carbon bearing chlorine. This closes the ring, giving rise to the cyclic ketene-*N,O*-acetal **234**. This is followed by rapid *N*-debenzoylation leading to cyclic ketene-*N,O*-acetal **291**. This is simply a postulated mechanism, which outlines the rationale for originally trying this method to make **291**. It is also possible that *N*-debenzoylation occurred first, followed by ring closure. In that case, *O*-debenzoylation step would be the last step.



Scheme 6.2 A possible route to cyclic ketene-*N,O*-acetal **291** from **244**

Both cyclic ketene-*N,O*-acetal **291** and its deprotonated form, anion **293**, have three nucleophilic sites, the ring nitrogen, the β -carbon and the oxygen of the β -carbonyl

function (Figure 6.1). A few reactions were conducted to explore their regioselectivity towards benzoyl chloride and phenyl chloroformate.

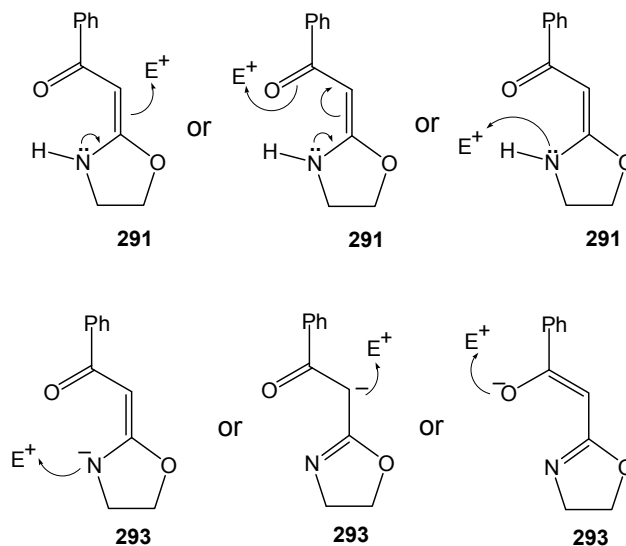
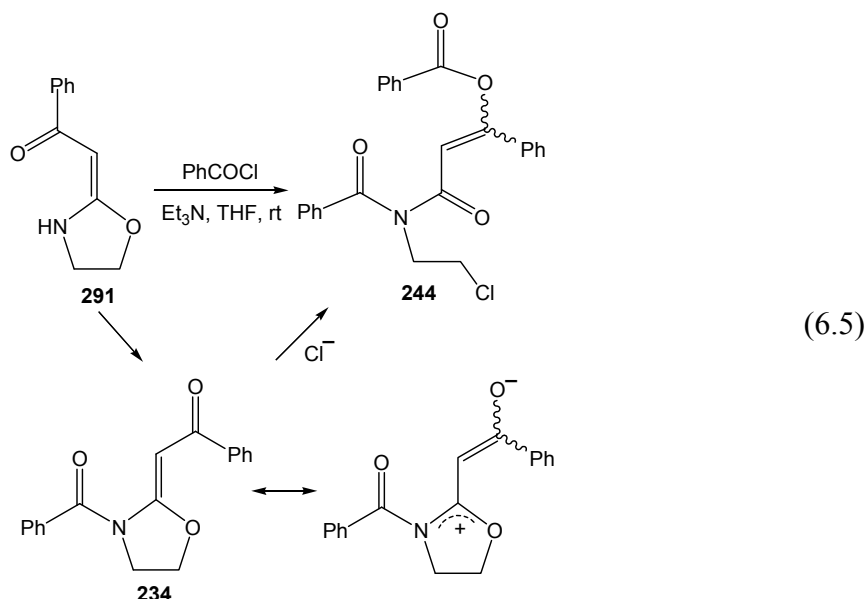


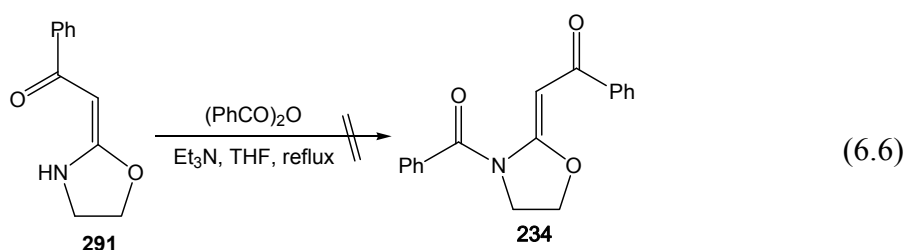
Figure 6.1 **291** and its deprotonated form **293** are ambident nucleophiles

Cyclic ketene-*N,O*-acetal **291** was reacted with benzoyl chloride in THF/ Et_3N in an attempt to form *N,C*-bisbenzoylated cyclic ketene-*N,O*-acetal **234** by *N*-benzoylation (Equation 6.5). One equivalent benzoyl chloride, diluted in THF solvent, was added over 5 h to **291** at room temperature in order to avoid tribenzoylation and ring opening to **244** and favor formation of **234**. However, only trace amount of ring-opened **244** and no **234** was obtained. Most of the starting material **291** was recovered (Equation 6.5). *N,C*-Dibenzoylated product **234** was presumably formed but it rapidly reacted further with very low concentrations of benzoyl chloride even at room temperature to form ring-opened product **244**. This suggests that *O*-benzoylation of **234** occurs faster than *N*-benzoylation of **291**. This emphasizes the ability of **234** to act as a “push-pull”

electronic system, placing negative charge on the β -keto carbonyl oxygen, thereby enhancing its nucleophilicity.

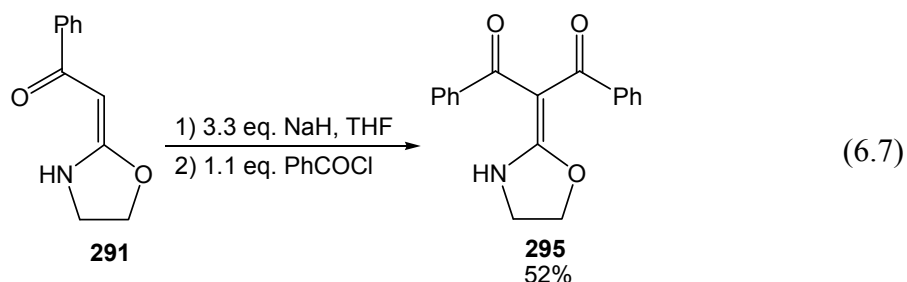


The failure to isolate **234** in the benzoylation of cyclic ketene-*N,O*-acetal **291** with benzoyl chloride prompted us to try benzoylation of **291** with benzoic anhydride (Equation 6.5). The benzoate anion, less nucleophilic than chloride, so it may not cause ring opening of **234**. However, after refluxing for 10h in THF in the presence of Et₃N, only the starting material **291** was recovered (Equation 6.6).

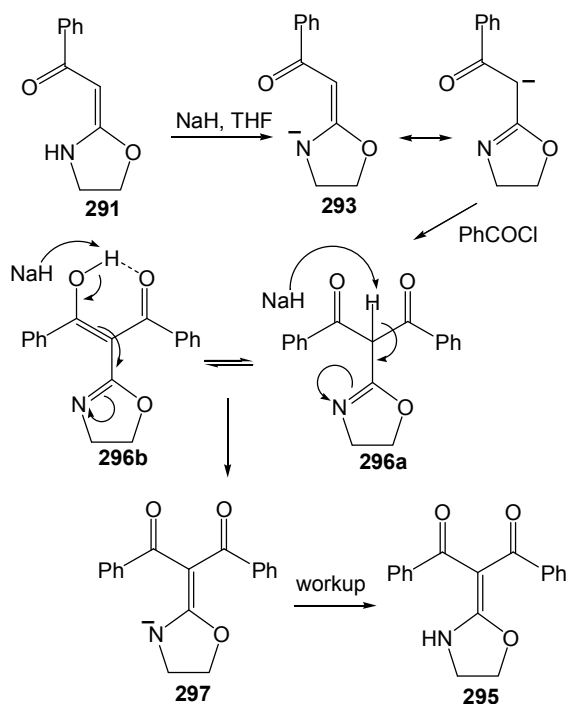


The reactivity of ambident anion **293** was investigated next. Cyclic ketene-*N,O*-acetal **291** was first deprotonated by excess sodium hydride to form ambident anion **293** (Equation 6.6). Then **293** was reacted with one equivalent of benzoyl chloride to explore which site would react with the electrophile. Benzoylation occurred at the β -carbon to

give the β,β -dibenzoylated cyclic ketene-*N,O*-acetal **295** in an isolated yield of 52 % (Equation 6.7).

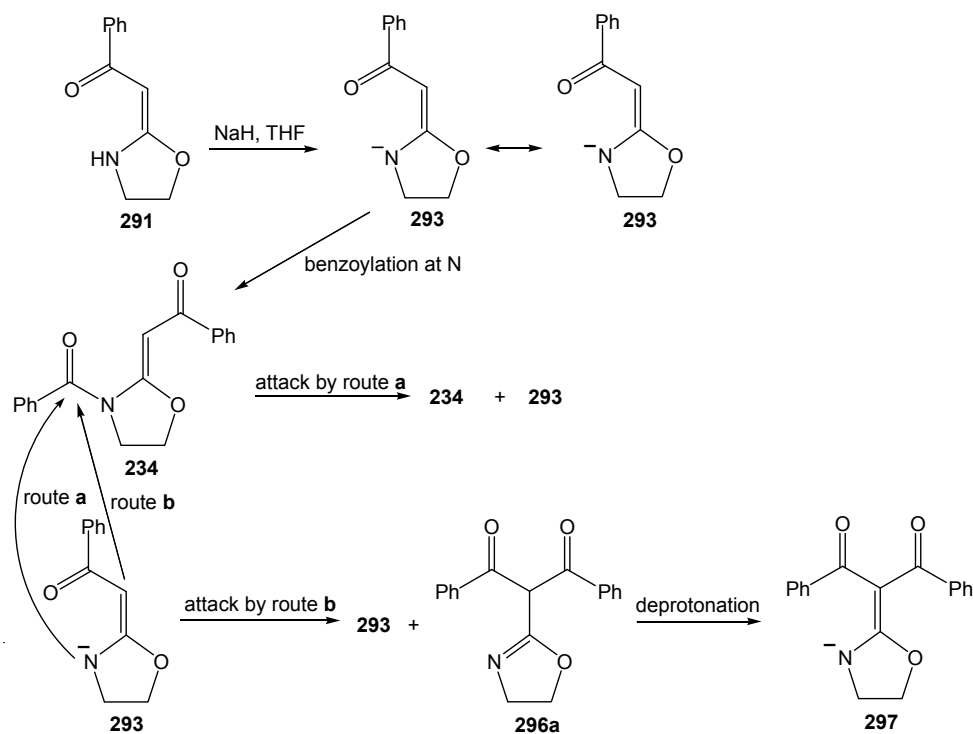


A mechanism is proposed in Scheme 6.3. Sodium hydride deprotonated the NH function of **291** to form the ambident anion **293**. The β -carbon site of **293** reacted with benzoyl chloride to give adduct **296** (tautomers **296a** and **296b**). The remaining sodium hydride deprotonated the β -proton of **296a**, generating the stable anion **297**. Aqueous workup protonated **297** to form **295**. Interestingly, tautomer **295** was obtained from **297** and not **296a**. It should be noted that sodium hydride only reacted as an acid scavenger in this reaction system. Nucleophilic attack by the hydride ion on the carbonyl carbon of benzoyl chloride does not occur because the hydride ion's filled 1s orbital is too small to interact easily with the more diffuse LUMO (π^*) of the carbonyl group.⁵⁵



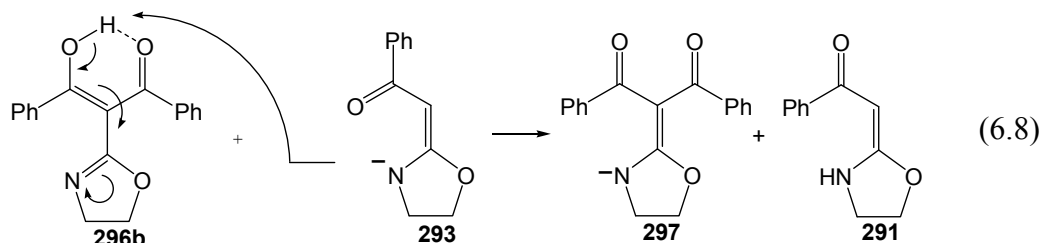
Scheme 6.3 A suggested route to cyclic ketene-*N,O*-acetal tautomer **295** from **291**

N,C-Dibenzoylation product **234** and *N,C,O*-tribenzoylation product **244** (see Equation 6.5) were not isolated from the reaction system in Scheme 6.3. It is possible that **234** did form via *N*-benzoylation of **293** (Scheme 6.4). However, if **234** was formed, it could further react with the ambident anion **293**. If **293** attacks the amide carbonyl carbon of **234** via its ring nitrogen (route **a** in Scheme 6.4), both **234** and **293** are simply regenerated and no net change in the system occurs. However, if **293** attacks **234** via its β -carbon (route **b** in Scheme 6.4), β,β -dibenzoyl product, **296a**, will form. Subsequent deprotonation of **296a** by sodium hydride gives stable anion **297**. This could explain why *N,C*-dibenzoylated product, **234**, was not observed.

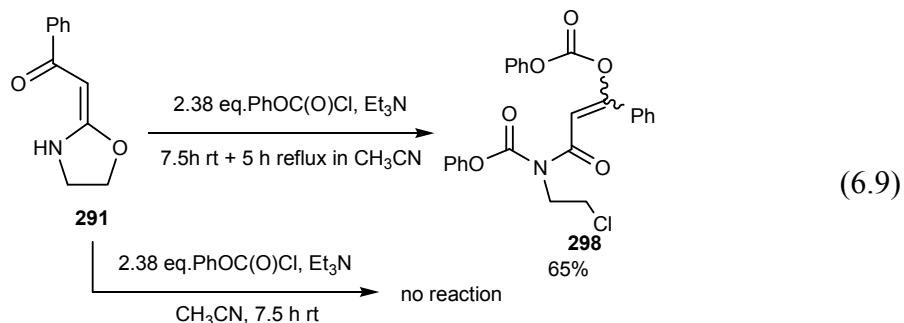


Scheme 6.4 Reason why *N,C*-dibenzoylation product **234** is not observed

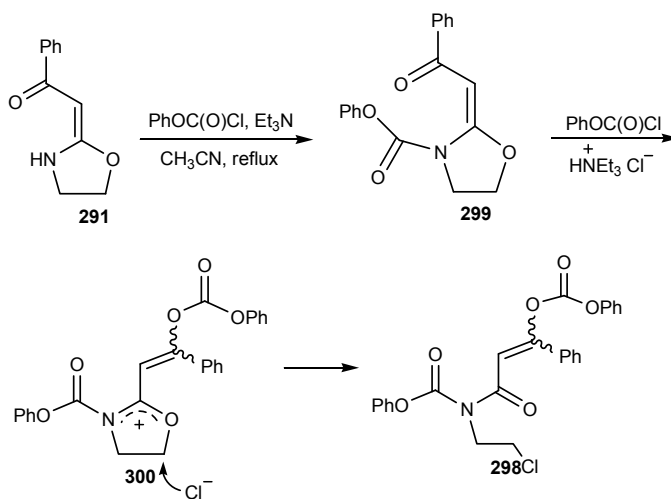
An anticipated side reaction is that between the ambident anion **293** and **296a**. The β -proton of **296a** is very acidic because of the two flanking electron withdrawing benzoyl functions and the adjacent imine function. This proton would be easily removed by **293** to form **297** (Equation 6.8). That is, in addition to reacting with benzoyl chloride to form **296a**, **293** also would react with **296a** to form anion **297**. Thus, this portion of **293** would be converted back to **291**. This accounts for the fact that some starting material **291** was recovered after aqueous workup and separation.



Cyclic ketene-*N,O*-acetal **291** was reacted with phenyl chloroformate in CH₃CN/Et₃N. No reaction was detected by TLC analysis when the mixture was stirred at room temperature for 7.5h. Upon refluxing for 5 h, however, ring-opened carbonic acid 3-[(2-chloroethyl)-phenoxy-carbonyl-amino]-3-oxo-1-phenylpropenyl ester phenyl ester (**298**), was obtained in 65 % yield (Equation 6.9).

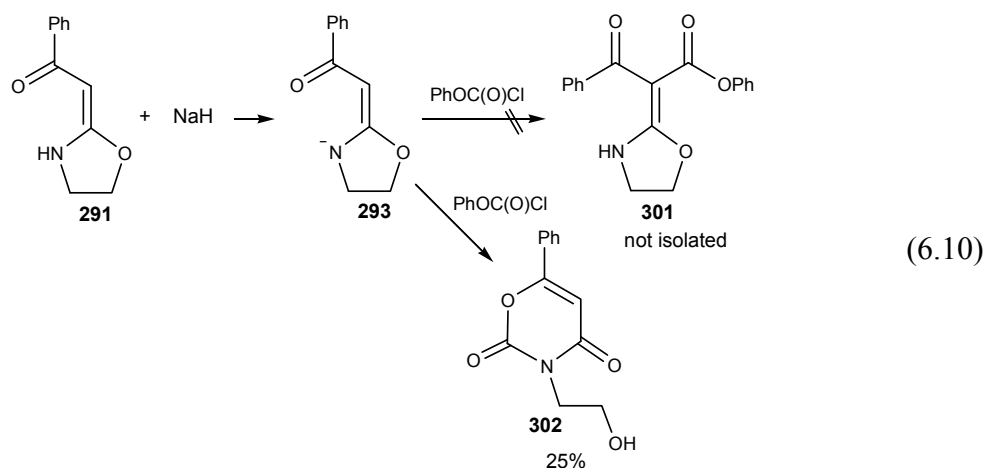


Formation of **298** is similar to the benzoylation of **291** to give **244** (Equation 6.5). It is suggested that nucleophilic attack of **291** on phenyl chloroformate occurs at the ring nitrogen, giving rise to **299** as an intermediate. Subsequent β -keto oxygen phenoxycarbonylation leads to **300**.



Scheme 6.5 A suggested route to carbonic acid 3-[(2-chloroethyl)-phenoxy-carbonyl-amino]-3-oxo-1-phenylpropenyl ester phenyl ester (**298**)

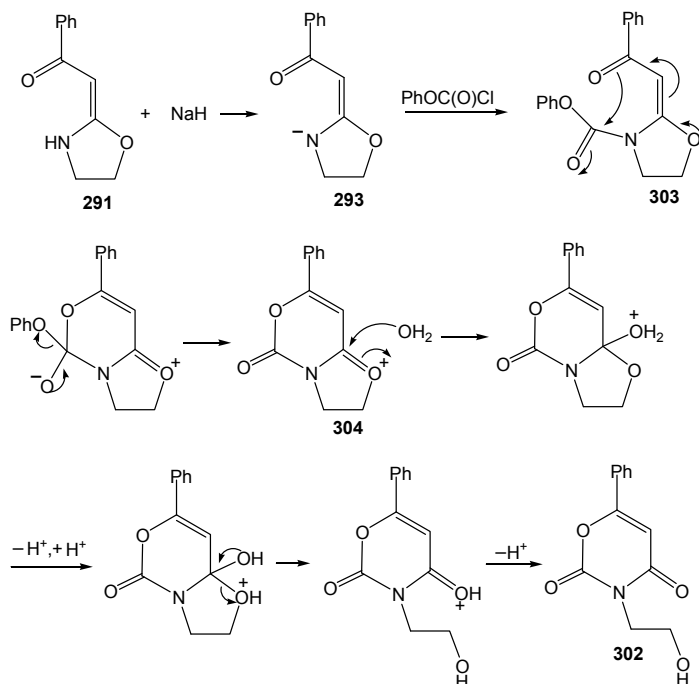
The ambident anion **293** was also reacted with the weaker electrophile, phenyl chloroformate (Equation 6.10). Surprisingly, the expected C-alkoxycarbonylation adduct **301** was not isolated. Instead, the completely unforeseen product, 3-(2-hydroxyethyl)-6-phenyl-[1,3]oxazine-2,4-dione, **302**, a highly functionalized heterocycle, was formed in 25 % yield. In addition, the starting material **291** was recovered in 12 % yield. No attempts have been made to optimize this reaction.



The ring system **302** has never been observed in any reaction product of a cyclic ketene-*N,O*-acetal previously. A mechanism for the formation of **302** is proposed in Scheme 6.6. Anion **293** could react at its ring nitrogen with phenyl chloroformate to form **303**. This could be followed by intramolecular nucleophilic attack of the carbonyl oxygen on the carbamate carbonyl carbon to form fused ring oxazolinium cation **304**. Hydrolysis of **304** would provide ring-opened product **302**.

There is no evidence that the β,β -disubstituted **301** (Equation 6.10) is ever formed in this reaction. This is in sharp contrast to the formation of the β,β -dibenzoylated **295** from the reaction of anion **293** with benzoyl chloride (Scheme 6.3). Phenyl chloroformate is a harder electrophile than iodomethane and may preferentially react with the ring

nitrogen site instead of the softer β -carbon site to form **300**. Transformation of **300** to **301** followed by hydrolysis during workup afforded **302**.



Scheme 6.6 A suggested route to **302**

In summary, β -benzoyl cyclic ketene-*N,O*-acetal, where the ring nitrogen bears a hydrogen, is an ambident nucleophile. It reacted with benzoyl chloride to give *N*-benzoylation followed by β -keto *O*-benzoylation and chloride ring opening. It reacted with phenyl chloroformate similarly to give ring-opened product. The ambident anion, generated from deprotonation of this β -keto five-membered cyclic ketene-*N,O*-acetal, reacted with benzoyl chloride to give β,β -bisbenzoyl cyclic ketene-*N,O*-acetal, and reacted with phenyl chloroformate giving rise to a substituted [1,3]oxazine-2,4-dione structure. This is another example of heterocycle synthesis from cyclic ketene acetals.

Experimental

Preparation of 2-oxazolidin-2-ylidene-1-phenylethanone (**291**) from debenzoylation of 3-[benzoyl-(2-chloroethyl)-amino]-3-oxo-1-phenylpropenyl benzoate (**244**)

Compound **244** (1.25 g, 2.88 mmol, 1 eq.) was dissolved in 50 mL of refluxing anhydrous methanol and cooled to room temperature. KOH (0.53 g, 8.5 mmol, 3.0 eq.), dissolved in 10 mL anhydrous methanol, was added dropwise over two minutes to **244**. A yellow color was seen immediately. After 12.5 h stirring at room temperature, rotary evaporation was employed to remove the solvent, and 23 mL DCM and 30 mL deionized water were added and the mixture was stirred. Sulfuric acid (1.0 M) was used to neutralize the mixture. The organic layer was further washed with 40 mL water, dried with anhydrous Na₂SO₄, and concentrated by rotary evaporation. The crude product was subjected to column chromatography (silica gel as stationary phase, eluenting solvent was acetone/hexanes (1:2 volume ratio)). The product **291** is a white solid (0.24 g, 1.3 mmol, 44 % yield). The crystal structure of **291** (Figure 6.2) showed that the distance between hydrogen on the ring nitrogen and the β-carbonyl oxygen is 2.167 Å, suggesting that there is an intramolecular hydrogen bond present in the solid state.

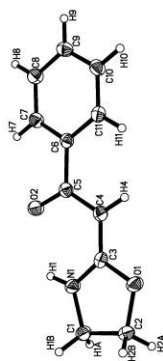


Figure 6.2 The crystal structure of 2-oxazolidin-2-ylidene-1-phenylethanone (**291**).
CCDC: 796899

^1H NMR (300 MHz, CDCl_3): δ 3.80 (t, $>\text{NCH}_2-$, $J = 8.0$ Hz, 2H), 4.48 (t, $-\text{CH}_2\text{O}-$, $J = 8.0$ Hz, 2H), 5.64 (s, $=\text{CH}(\text{COPh})$, 1H), 7.34-7.92 (aromatic, 5H), 10.00 (s, br, $>\text{NH}$, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 187.5 ($\text{N}, \text{O}>\text{C}=\text{}$), 170.6 ($-\text{COPh}$), 139.9, 130.5, 128.1, 126.7 (aromatic), 74.0 ($=\text{C}(\text{COPh})$), 67.3 ($-\text{OCH}_2-$), 43.0 ($\text{N}-\text{CH}_2-$). IR (neat, cm^{-1}): 3316, 2898, 1619, 1583, 1512, 1483, 1240, 1036, 965, 931, 860, 741, 690, 634. mp 105-106 $^\circ\text{C}$.

Benzoylation of 2-oxazolidin-2-ylidene-1-phenylethanone (**291**) with benzoyl chloride

Benzoyl chloride (0.123 g, 0.87 mmol, 1.0 eq., diluted in 23 mL CH_3CN) was added dropwise to the solution of cyclic ketene-*N,O*-acetal **291** (0.163 g, 0.86 mmol, 1 eq.), *N,N*-diisopropylethylamine (0.143 g, 1.10 mmol, 1.27 eq.) and 11 mL dried CH_3CN , over 5 h at room temperature, under nitrogen protection. After 2h stirring at room temperature, the reaction was stopped and rotary evaporation was employed to remove solvent. Then 15 mL DCM and 75 mL deionized water were added and the mixture stirred. The organic layer was further washed with 40 mL water, dried with anhydrous Na_2SO_4 and concentrated by rotary evaporator. The mixture was subjected to column chromatography (silica gel as stationary phase, eluenting solvent was acetone/hexanes (1:2 volume ratio). A trace amount of ring-opened **244** was obtained and most of the starting material **291** was recovered.

Benzoylation of cyclic ketene-*N,O*-acetal **291** with benzoic anhydride

Benzoic anhydride (0.087 g, 0.38 mmol, 2.0 eq.) was added in one portion to the solution of cyclic ketene-*N,O*-acetal **291** (0.036 g, 0.19 mmol, 1 eq.), triethylamine (0.044 g, 0.43 mmol, 2.27 eq.) and 7 mL dried THF. Refluxing of the mixture for 10 h

under nitrogen protection gave no product, monitored by TLC. Only the starting materials were recovered.

DMAP-catalyzed benzylation of cyclic ketene-*N,O*-acetal **291** with benzoic anhydride

Cyclic ketene-*N,O*-acetal **291** (0.123 g, 0.65 mmol, 1 eq.), 25 mL dried CH₃CN, triethylamine (0.101 g, 0.99 mmol, 1.53 eq.) and benzoic anhydride (0.303 g, 1.32 mmol, 2.04 eq.) were added to a 100 mL flask. A clear solution was obtained. DMAP (0.024 g, 0.30 eq.) was added in one portion. Refluxing of the mixture for 7 h under nitrogen protection gave no product, monitored by TLC. Only the starting materials were recovered.

Preparation of 2-oxazolidin-2-ylidene-1,3-diphenylpropane-1,3-dione (**295**) from benzylation of ambident anion **293**

Sodium hydride (0.36 g, 9.0 mmol, 60 % pure, dispersed in mineral oil, 3.3 eq.) was added in one portion to 0.52 g (2.8 mmol) cyclic ketene-*N,O*-acetal **291** in dried THF (28.5 mL). Bubbles evolve and leave the reaction system through a bubbler. After 7 h 20 min stirring at room temperature, benzoyl chloride (0.44 g, 3.1 mmol) in THF (22 mL) was added dropwise over 1 h. Bubbles were seen. The mixture was stirred for 8 h. Rotary evaporation was employed to remove the solvent, followed by washing with 23 mL DCM and 35 mL deionized water. Sulfuric acid (1.0 M) was used to neutralize the mixture. The organic layer was further washed with water (40 mL), dried with anhydrous Na₂SO₄, concentrated by rotary evaporator. The mixture was subjected to column chromatography (silica gel as stationary phase, eluenting solvent was acetone/hexanes (1:2 then 1.2:1 volume ratio)). The product 2-oxazolidin-2-ylidene-1,3-diphenylpropane-1,3-dione (**295**),

is a white solid (0.42 g, 1.4 mmol, 52 % yield). Starting material **291** (0.073 g, 0.39 mmol, 0.14 eq.) was also recovered in 14 % yield. ¹H NMR (300 MHz, CDCl₃): δ 3.82 (t, >NCH₂-, J = 8.6 Hz, 2H), 4.51 (t, -CH₂O-, J = 8.6 Hz, 2H), 7.00-7.95 (aromatic, 10H), 10.65 (>NH). ¹³C NMR (75 MHz, CDCl₃): δ 193.7 (N,O>C=), 170.6 (-COPh), 141.3, 130.0, 128.0, 127.6 (aromatic), 95.8 (=C(COPh)₂), 68.4 (-OCH₂-), 42.6 (N-CH₂-). IR (neat, cm⁻¹): 3274, 1599, 1577, 1533, 1477, 1444, 1360, 1340, 1213, 1099, 966, 953, 870, 747, 708, 666. mp 205-206 °C.

Preparation of carbonic acid 3-[(2-chloroethyl)-phenoxy-carbonyl-amino]-3-oxo-1-phenylpropenyl ester phenyl ester (**298**) by benzylation of 2-oxazolidin-2-ylidene-1-phenylethanone (**291**) in CH₃CN

2-Oxazolidin-2-ylidene-1-phenylethanone (**291**) (0.095 g, 0.50 mmol, 1 eq.) was placed in a 50 mL flask, followed by dried CH₃CN (7.4 mL) and Et₃N (0.152 g, 1.50 mmol, 2.97 eq.). Phenyl chloroformate (0.193 g, 1.20 mmol, 2.38 eq.), was added dropwise over 5 min. The mixture was stirred at room temperature for 7.5 h under nitrogen. TLC showed no reaction. The mixture was then refluxed for 5 h. TLC showed the was consumed totally. A yellow solution was obtained. Solvent was removed by rotary evaporation. Dichloromethane (8 mL) and saturated NaHCO₃ (14 mL) were added to the residue and the mixture was stirred for 10 min. The organic layer was washed further with water (2 x 20 mL), and dried over anhydrous Na₂SO₄. After concentrating by rotary evaporation, the crude product was purified by flash column chromatography over silica gel, using acetone/hexanes (1:2 volume ratio) as the eluting solvent. Carbonic acid 3-[(2-chloroethyl)-phenoxy-carbonyl-amino]-3-oxo-1-phenylpropenyl ester phenyl ester (**298**) (white solid, mp 119-120 °C, 0.153 g, 0.32 mmol) was obtained, yield 65.3 %. ¹H

NMR (300 MHz, CDCl₃): δ 7.09-7.78 (m, aromatic H, 15H), 6.34 (s, -CH=(Ph)OC(O)OPh, 1H), 4.26 (t, J = 4.5 Hz, -CH₂-Cl, 2H), 3.76 (t, J = 4.5 Hz, >N-CH₂-, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 161.9 (PhOC(O)N< or -OC(O)OPh or >NC(O)CH= or =C(Ph)OC(O)OPh), 161.1 (PhOC(O)N< or -OC(O)OPh or >NC(O)CH= or =C(Ph)OC(O)OPh), 154.0 (PhOC(O)N< or -OC(O)OPh or >NC(O)CH= or =C(Ph)OC(O)OPh), 151.8 (PhOC(O)N< or -OC(O)OPh or >NC(O)CH= or =C(Ph)OC(O)OPh), 151.4 (aromatic), 150.8 (aromatic), 148.3 (aromatic), 132.5 (aromatic), 129.4 (aromatic), 129.0 (aromatic), 128.4 (aromatic), 126.1 (aromatic), 126.0 (aromatic), 124.8 (aromatic), 121.6 (aromatic), 120.7 (aromatic), 97.3 (=C(Ph)OC(O)OPh), 42.5 (>N-CH₂- or -CH₂-Cl), 39.5 (>N-CH₂- or -CH₂-Cl). IR (neat, cm⁻¹): 3105, 1763, 1686, 1641, 1448, 1422, 1392, 1371, 1077, 915, 822, 751, 684, 638.

Preparation of 3-(2-hydroxyethyl)-6-phenyl-[1,3]oxazine-2,4-dione (**302**) from the reaction of ambident anion (**293**) with phenyl chloroformate

Sodium hydride (0.22 g, 5.5 mmol, 60 % pure, dispersed in mineral oil, 2.9 eq.) was added in one portion to cyclic ketene-*N,O*-acetal **291** (0.36 g, 1.9 mmol) in dried THF (47 mL). Bubbles evolve and leave the reaction system through a bubbler. After stirring 4.5 h at room temperature, phenyl chloroformate (0.35 g, 2.2 mmol, 1.1 eq.) in THF (16 mL) was added dropwise over 37 min. The mixture was stirred 3 h. Rotary evaporation was employed to remove solvent, and DCM (15 mL) plus deionized water (25 mL) were added and the mixture stirred. Sulfuric acid (1.0 M) was used to neutralize the mixture. The organic layer was further washed with water (25 mL), dried with anhydrous Na₂SO₄ and concentrated by rotary evaporation. The mixture was subjected to column chromatography (silica gel as stationary phase, solvent was acetone/hexanes (1:2 volume

ratio). The product, 3-(2-hydroxyethyl)-6-phenyl-[1,3]oxazine-2,4-dione (**302**), is a white solid (0.12 g, 0.52 mmol, 27 % yield). The starting material **291** (0.044 g, 0.23 mmol, 0.12 eq.) was also recovered in 12 % yield. ^1H NMR (300 MHz, CDCl_3): δ 2.56 (s, CH_2OH , 1H), 3.93 (t, $>\text{NCH}_2$ -, 2H), 4.18 (t, $-\text{CH}_2\text{O}$ -, $J = 5.3$ Hz, 2H), 6.39 (s, $\text{Ph}, \text{O}>\text{C}=\text{CH}$ -, 1H), 7.45-7.95 (aromatic, 5H). ^{13}C NMR (75 MHz, CDCl_3): δ 162.4 (($\text{C}=\text{O}$)-O- or ($\text{C}=\text{O}$)-N<), 162.0 (($\text{C}=\text{O}$)-O- or ($\text{C}=\text{O}$)-N<), 149.1 ($\text{Ph}, \text{O}>\text{C}=\text{CH}$ -), 132.6, 129.1, 128.6, 126.1 (aromatic), 97.6 ($=\text{CHC}(\text{O})$ -), 60.2 ($-\text{CH}_2\text{OH}$), 44.1 ($>\text{NCH}_2$ -). IR (neat, cm^{-1}): 3460, 3377, 1748, 1734, 1679, 1661, 1632, 1447, 1395, 1355, 1048, 772, 753, 685. mp 137-138 $^\circ\text{C}$. The crystal structure of **302** is shown in Figure 6.3.

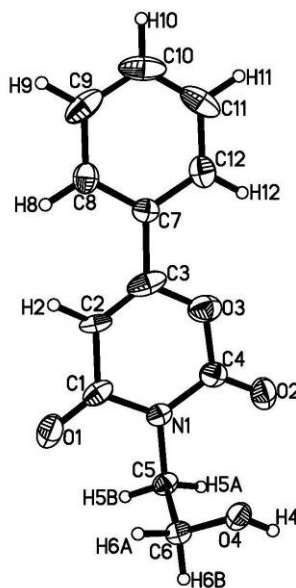


Figure 6.3 The crystal structure of 3-(2-hydroxyethyl)-6-phenyl-[1,3]oxazine-2,4-dione (**302**). CCDC: 796903

REFERENCES

- [1] McElvain, S. M.; Curry, M. J. *J. Amer. Chem. Soc.* **1948**, *70*, 3781.
- [2] McElvain, S. M. *Chem. Rev.* **1949**, *45*, 453 and reference cited therein.
- [3] Beyerstedt, F.; McElvain, S. M. *J. Amer. Chem. Soc.* **1936**, *58*, 529.
- [4] (a) Williams, D. J. *Angew. Chem. Int. Ed.* **1984**, *23*, 690. (b) Kanis, D. R.; Ratner, M. A.; Marks, T. J. *Chem. Rev.* **1994**, *94*, 195.
- [5] Wu, Z.; Stanley, R. R.; Pittman, C. U., Jr. *J. Org. Chem.* **1999**, *64*, 8386.
- [6] Meyers, A. I.; Nazareno, N. *J. Amer. Chem. Soc.* **1972**, *94*, 3243.
- [7] Zhou, A.; Pittman, C. U., Jr. *J Comb Chem.* **2006**, *8*, 262.
- [8] Sanda, F.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *39*, 265.
- [9] (a) Zhu, P. C.; Pittman, C. U. Jr. *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 169. (b) Cao, L.; Wu, Z.; Zhu, P. C. *Polym. Prepr.* **1999**, *39*, 406. (c) Cao, L.; Wu, Z.; Pittman, C. U., Jr. *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 2841. (d) Cao, L.; Pittman, C. U. Jr. *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 2823. (e) Wu, Z.; Cao, L.; Pittman, C. U. Jr. *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 861. (f) Wu, Z.; Cao, L.; Zhu, P. C. *Polym. Prepr.* **1997**, *38*, 121. (g) Wu, Z. Ph.D Dissertation, Mississippi State Univ. **1997** (h) Zhu, P. C.; Pittman, C. U. Jr. *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 73. (i) Liu, Y.; Pittman, C. U., Jr. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 3655. (j) Zhu, P. C.; Wu, Z.; Pittman, C. U., Jr. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 485. (k) Liu, Y.; Keller, C. E.; Pittman, C. U., Jr. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 3707.
- [10] Yokozawa, T.; Hayashi, R.; Endo, T. *Macromolecules* **1992**, *25*, 3313.
- [11] Endo, T. *Jpn. Kokai Tokkyo Koho* **1985**, JP 60223827.
- [12] Fukuda, H.; Oda, M.; Endo, T. *Macromolecules* **1996**, *29*, 3043.
- [13] Fukuda, H.; Oda, M.; Endo, T. *Macromolecular Rapid Commun* **1998**, *19*, 149.

- [14] Zhou, A.; Cao, L.; Li, H.; Liu, Z.; Cho, H.; Henry, W. P.; Pittman, C. U., Jr. *Tetrahedron* **2006**, *62*, 4188. (b) Zhou, A.; Cao, L.; Li, H.; Liu, Z.; Pittman, C. U., Jr. *Synlett* **2006**, 201. (c) Li, H. MS Thesis, Mississippi State University **2000** (d) Cao, L. PhD dissertation, Mississippi State University **1998** (e) Zhou, PhD dissertation, Mississippi State University **2004**.
- [15] Ye, G.; Henry, W. P.; Chen, C.; Zhou, A.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2009**, *50*, 2135.
- [16] Huang, Z.; Yang, L. K. *Heteroatom Chem.* **1992**, *3*, 487.
- [17] Fukuda, H.; Oda, M.; Taketa, T.; Endo, T. *Macromolecules*, **2000**, *33*, 6211.
- [18] Korshin, E. E.; Sabirova, L. I.; Levin, Y. A.; Arbuzov, A. E. *Izv. Akad. Nauk, Ser. Khim.* **1994**, *8*, 1509.
- [19] Zhou, A.; Pittman, C. U., Jr. *Synthesis* **2006**, 37.
- [20] Zhou, Aihua; Pittman, Charles U. Jr. *Tetrahedron Letters* **2004**, *45*, 8899.
- [21] (a) Zhou, A.; Pittman, C. U. Jr. *Tetrahedron Letters* **2005**, *46*, 3801. (b) Zhou, A.; Moses N.; Pittman, C. U. Jr. *Tetrahedron*, **2006**, *62*, 4093.
- [22] Miller, R.; Abaecherli, C.; Said, A.; Jackson, B. *Ullmann's Encyclopedia of Industrial Chemistry*, DOI: 10.1002/14356007.a15_063
- [23] Tohda, Y.; Morikawa, M.; Kawashima, T.; Ariga, M.; Mori, Y. *Chem. Lett.* **1986**, 273.
- [24] Zhou, A.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2005**, *46*, 2045.
- [25] Ye, G.; Chen, C.; Chatterjee, S.; Collier, W. E.; Zhou, A.; Song, Y.; Beard, D. J.; Pittman, C. U., Jr. *Synthesis* **2010**, 141.
- [26] Ye, G.; Chatterjee, S.; Zhou, A.; Barker, B. L.; Chen, C.; Song, Y.; Pittman, C. U., Jr. *Synthesis* **2010**, 1209.
- [27] Ye, G.; Zhou, A.; Henry, W. P.; Song, Y.; Chatterjee, S.; Beard D. J. and Pittman, C. U. Jr. *J. Org. Chem.* **2008**, *73*, 5170.
- [28] Godefroi, E. F. and Geenen, I. H. *J. Med. Chem.* **1975**, *18*, 530.
- [29] Chatterjee, S.; Ye, G.; Pittman, C. U. Jr. *Tetrahedron Lett.* **2010**, *51*, 1139.
- [30] Huang, Z.; Liu Z. R. *Chem. Ber.* **1989**, *122*, 95.

- [31] Tieman, C. H.; Kollmeyer, W. D.; Steven, S. A. *Ger. Offen* , 2445421 (Chem. Abstr. 1975, 83, 97297b).
- [32] Huang, Z.; Tzai, L. *Chem. Ber.* **1986**, *119*, 2208.
- [33] Jones, R. C. F.; Smallridge, M. J. *Tetrahedron Lett.* **1988**, *29*, 5005.
- [34] Jones, R. C. F.; Hirst, S. C. *Tetrahedron Lett.* **1989**, *30*, 5361.
- [35] Viswanathan, N. I.; Balakrishnan, V. *J Chem. Soc., Perkin Tran. I*, **1979**, 2361.
- [36] Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron*, **1990**, *46*, 5423.
- [37] Gruseck, U.; Heuschmann, M. *Tetrahedron Lett.* **1987**, *28*, 6027.
- [38] Yin, Y.; Wang, M.; Liu, Q.; Hu, J.; Sun, S.; Kang, J. *Tetrahedron Lett.* **2005**, *46*, 4399.
- [39] Carey, F. A.; Court, A. J. *J. Org. Chem.* **1972**, *37*, 4474.
- [40] Danishefsky, S.; McKee, R.; Singh, R. K. *J. Org. Chem.* **1976**, *41*, 2934.
- [41] Ley, S. V.; Mitchell, W. L.; Radhakrishnan, T. V.; Barton, D. H. R. *J. Chem. Soc., Perkin Tran. I* **1981**, *5*, 1582.
- [42] Bohme, H.; Haake, M. *Iminium Salts in Organic Chemistry*, **1977**, John Wiley & Sons Inc, p219.
- [43] E. Pretsch, P. Bühlmann, C. Affolter, *Structure Determination of Organic Compounds: Tables of Spectral Data*, Springer, **2000**, p296.
- [44] (a) Dreme, M.; Le Perchec, P.; Garapon, J.; Sillion, B. *Tetrahedron Lett.* **1982**, *23*, 73. (b) Zhu, P. C.; Lin, J.; Pittman, C. U., Jr. *J. Org. Chem.* **1995**, *60*, 5729.
- [45] Kumar, U. K. S.; Ila H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193.
- [46] A twist angle is defined as the angle between the bisectors of the 1,1- and the 2,2-substituents on a Newman diagram projecting down the C=C bond of the alkene. See: (a) Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169 (b) Ye, G.; Chatterjee, S.; Li, M.; Zhou, A.; Song, Y.; Barker, B. L.; Chen, C.; Beard, D. J.; Henry, W. P.; Pittman, C. U., Jr. *Tetrahedron* **2010**, *66*, 2919.
- [47] Michael J. P.; Chang S.; Wilson C. *Tetrahedron Lett.* **1993**, *34*, 8365.
- [48] Sheldrick, G. M. *Acta Cryst. A* **2008**, *64*, 112.

- [49] Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkowicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, 85, 207.
- [50] Tohda, Y.; Kawashima, T.; Ariga, M.; Akiyama, R.; Shudoh, H.; Mori, Y. *Bulletin of the Chemical Society of Japan* **1984**, 57, 2329.
- [51] Morimoto T.; Sekiya, M. *Chem. Pharm. Bull.* **1977**, 25, 1230.
- [52] Brunerie, P.; Célérier, J. P.; Petit H.; Lhommet G. *J. Heterocyclic Chem.* **1986**, 23, 1183.
- [53] (a) Brown, H. C.; Ham, G. *J. Am. Chem. Soc.* , **1956**, 78, 2735. (b) Brown, H. C.; Brewster, J. H.; Shechter, H. *J. Am. Chem. Soc.* , **1954**, 76, 467. (c) Brown, H. C.; Borkowski, M. *J. Am. Chem. Soc.*, **1952**, 74, 1894. (d) Brown, H. C. *J. Org. Chem.*, **1957**, 22, 439.
- [54] Huang Z.; Zhang P. *Chem Ber*, **1989**, 122, 2011.
- [55] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry* , Oxford University Press, 1 edition, **2000**, p139.